ELECTROSPRAY FOURIER TRANSFORM ION CYCLOTRON RESONANCE MASS SPECTROMETRY OF ORGANIC SALTS

By

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The electrospray ionization method, with its "soft" ionization power, when combined with the exceptional features of Fourier transform ion cyclotron resonance mass spectrometry, such as ultrahigh mass resolution, accurate and stable mass calibration, multiple stages of collisionally activated dissociation allowing tandem MS/MS, and extremely long ion storage times, can provide an excellent way of studying the properties of chemical compounds. Gas phase investigations of reaction mechanisms provide many advantages as compared to the familiar and much studied solution phase chemistry, including freedom from interferences (i.e. solvent effects) and simplicity of the reaction scheme. This research has concentrated on the properties of singly and multiply charged organic salts such as pyridinium and sulfonium salts. The effect of structural variation, such as presence of electron-donor and electron-acceptor substituents, on the dissociation pathways has been investigated *via* collisionally activated dissociation (CAD) reactions. Ion-molecule reactions have been performed for identification of nucleophilic substitution reaction mechanisms (S_N1 *vs.* S_N2-type reactions). A new general way of monitoring reactions in the gas phase has been proposed and applied in the prediction of dissociation rate constants for the pyrolysis of esters and calculation of relative threshold fragmentation energies, as a measurement of stability, for confirmation of the controversial theory of carbon-radicals stabilization.

CHAPTER 1

GENERAL DISCUSSION

1.1. Mass Spectrometry and the Gas Phase Investigation of the Cations of Organic Salts

Mass spectrometry has long been accepted as an excellent method for studying physical and chemical properties of materials, clusters, atoms, and particles. Due to the sensitivity and accuracy that can be obtained, mass spectrometry is widely considered the method of choice for the analysis and identification of unknown compounds and mixtures, especially for constituents present only in trace quantities.

Organic salts are among the many compounds whose properties in the gas phase can be studied utilizing mass spectrometric methods. Gas phase investigations of the relationship between chemical structures and reaction mechanisms provide many advantages compared to familiar and well studied solution phase techniques, such as freedom from interferences (*i.e.* solvent effects), simplicity, etc. There are numerous mass spectrometric reports describing studies of singly and multiply charged organic compounds where the charges are additionally introduced *via* protonation or complexation with metal ions such as Na^+, K^+, Ca^{+2}, etc. The studies in this thesis were concentrated on a different class of charged species, *i.e.* singly and multiply charged cations of organic salts that exist as such, rather than as cations formed by introduction of additional charges. A variety of mass spectrometric techniques, utilizing different ionization methods, have previously been used for the analysis of organic salts.

Among the most commonly used ionization techniques are FDMS (field desorption mass spectrometry) [75AC1165, 75JOC636, 83AC1310, 88TL3463, 88OMS705], LDMS (laser desorption mass spectrometry) [84AC866], SIMS (secondary ionization mass spectrometry) [80AC2054, 95JMS282, 94JPOC465], FABMS (fast atom bombardment mass spectrometry) [87JACS1980, 88OMS705, 91BSCB459, 93OMS71, 94JPOC465, 95JMS282], and ^{252}Cf PDMS (^{252}Cf plasma desorption mass spectrometry) [88TL3463, 88OMS705, 95JMS1187]. However, reports describing studies of singly and multiply charged organic salts using ESIMS (electrospray ionization mass spectrometry) [95JMS319, 95JPOC351] are still limited in number.

1.2. Experimental Discussion

1.2.1. Electrospray Ionization

Background. Electrospray ionization (ESI) is a "soft" ionization technique that allows pre-existing ions in solution to be transferred into the gas phase with minimal fragmentation. ESI was first described by Dole [68JCP2240, 73JAdCS73, 71B821], who began developing the technique in the late sixties. More recently, electrospray was shown to be an useful analytical tool by Fenn *et al.* [84JPC4451, 88JPC546, 89AC1702, 89S64]. The ESI technique has lately become very popular due to its ability to study a wide range of chemical systems and is considered to be one of the most versatile ionization techniques in existence [96MI1].

The mechanism of electrospray involves spraying the solution of interest from a needle kept at potential of a few kilovolts relative to the de-solvating capillary. The resulting field at the needle tip charges the surface of the emerging liquid, which is dispersed by Coulomb forces into a fine spray of charged droplets. Evaporation of the solvent from the droplets, caused by a counter-current drying gas or by passing through a heated capillary, results in a decrease in the diameter of the droplets and increase of the charge density on the surface of each droplet. Due to electrostatic repulsion, the droplets eventually subdivide as they move toward the inlet end, driven by the electric field, until the droplets are desorbed into ions [84JPC4451, 89S64, 90AC882, 93AC972A]. There is still some controversy regarding the detailed mechanism of producing gas-phase ions from the very small and highly charged droplets. Two mechanisms are usually cited for this process: (i) droplet fission at the Raleigh limit, proposed by Iribarne and Thomson [76JCP2287, 79JCP4451] and (ii) direct field evaporation of ions, originally assumed by Dole [68JCP2240] and further studied in detail by Röllgen [84JPC297, 89IJMSIPr139].

Electrospray ionization allows detection of both singly and multiply charged ions giving minimal fragmentation, which leads to a better and more accurate interpretation of the spectra. Various implementations of ESI have been coupled with virtually every type of mass spectrometer, including quadrupole, ion-trap, magnetic sector, time-of-flight, and Fourier transform ion cyclotron resonance. Electrospray mass spectrometry is applicable to relatively impure samples and multicomponent mixtures, and it is compatible with microanalytical separation techniques [91MSR359]. Electrospray ionization mass spectrometry has been shown to be an extremely powerful tool in the detection of high molecular weight species (reports have shown spectra of individual DNA ions with nominal molecular weight $M_r = 1.1 \times 10^8$ Da [95AC1159]) and it finds a broad application spectrum in the characterization of supramolecular complexes of biomolecules. Electrospray ionization provides advantages compared to most other known ionization techniques; its only major limitation is that electrospray is applied mainly to polar solutions. However, it has been shown that almost all solvents can be used.

Experimental setup used for all the experiments described herein. For the study of doubly charged cations described in Chapter 2, the ESI source was operated using a grounded needle and a metal coated glass capillary (0.5 mm I.D. x 150 mm) held at 4-5 kV potential. A nitrogen counter-current drying gas heated to 150 °C was used to desolvate the ions in the atmospheric ionization region as they passed between the needle and the capillary entrance. The pressure at the exit of the ESI source was held at 1.5×10^{-5} torr, maintained by a 800 L/s cryopump. For the studies described in Chapters 3-5, respectively, the experimental setup was improved *via* the introduction of a modified dual-stage hexapole ion-guide ESI source (Analytica of Branford, Branford, CN)*. The glass capillary with the nitrogen counter-current drying gas used in the first study was replaced by a heated metal capillary of similar dimensions. The metal capillary was mounted in a brass support and heated with a 200 W cartridge heater. The temperature was maintained at 120 °C using a RTD (Resistive Thermal Device) temperature controller which regulated the heater power supply. The modified source was operated without a counter-current drying gas. The change in the setup resulted in a significant improvement of the signal observed. The ions were sprayed from a needle maintained at a potential of +3.9 kV relative to the heated capillary. The pressure between the capillary exit and the first skimmer (1.0 mm diameter) was maintained at 1 mbar with a 500 L/min mechanical pump (Edwards, Model EM32). The pressure between the first skimmer and conductance limit (1 mm diameter) located in the center of the hexapole ion-guide was maintained at *ca.* 1×10^{-3} mbar with a turbo drag pump (Edwards, Model EXT250HI) as measured using a Pirani gauge (TPR 010, Balzers AG, Liechtenstein). The pressure after the ESI hexapole guide in the normal FTICR external source housing was *ca.* 1.0×10^{-6} mbar as pumped by the 800 L/s cryopump.

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* The experimental setup was modified by Dr. Clifford H. Watson and Mr. Joseph Nawrocki.

1.2.2. Laser Desorption Ionization as an Alternative Approach to Electrospray

Background. When the studies described in Chapters 3 and 4 were started, laser desorption was considered as an alternative ionization approach. The original plan was to acquire the necessary data using both ionization methods (laser desorption and electrospray) and to draw a comparison between the two. The laser desorption studies were performed on a 3T FTICR/MS instrument as described in the next section. There were no problems associated with sample preparation and detection of the ions of interest. However, when data for parent and fragment ions intensities were accumulated, numerous obstacles were encountered. The biggest problem came from data reproducibility, as a significant difference in the shot-to-shot ion intensities was observed. To some extent this problem was overcome by preparation of more uniform samples and by averaging data obtained from multiple scans. However, the final results were still insufficiently consistent and this approach was abandoned in favor of the electrospray ionization approach described above.

Experimental setup. All samples (1-5mg) used in the laser desorption experiments were dissolved in the appropriate solvents (ethanol, methanol, hexane or acetonitrile) (3-5 mL) and deposited on stainless steel probe tips with a pipette. The solid probe was inserted into the vacuum chamber only after all the solvent had evaporated and a thin (>1.0 mm thickness) homogeneous film of the sample had formed on the probe tip. The experiments began with a quench pulse applied to the trap plates to eject all ions from the cell followed by a focused CO_2 laser pulse that desorbed the samples. Standard excitation and detection techniques were used as described below. All laser desorption experiments were performed on a Nicolet FTICR/MS equipped with a IonSpec data station utilizing a 3T superconducting magnet. The vacuum chamber was pumped by a 300 L/s oil diffusion pump maintaining a background pressure of *ca.* 1-2 x 10^{-8} torr. After insertion of the solid probe in the vacuum chamber, the pressure was slightly increased up to *ca.* 2-5 x 10^{-8} torr. Ions formed by the laser desorption were trapped in a 2.54 cm cubic cell with a trap voltage of 2 V. The collisionally activated dissociation, excitation and detection processes are described below.

1.2.3. Fourier Transform Ion Cyclotron Resonance Mass Spectrometry

Background. Fourier transform ion cyclotron resonance mass spectrometry (FTICR/MS) was originally developed by Comisarow and Marshall in 1974 [74CPL282, 74CPL489, 74CJC1997]. FTICR/MS is an extremely versatile technique, as a wide variety of experiments can be performed in a very short period of time simply by changing the pulse sequence. FTICR/MS provides numerous advantages for studying gas phase reactions. Among them are ultra-high mass resolution and wide mass range [83IJMSIPh139] and accurate and stable mass calibration [83AC339]. Additionally, the ability to store ions for long times (> 1 min) [83IJMSIPh139] and manipulate and selectively detect ions present in extremely low concentrations [87MI1] have also been demonstrated. FTICR/MS allows the use of multiple stages of collisionally activated dissociation (CAD) leading to tandem mass spectrometry [82IJMSIP199].

In FTICR the mass resolution varies inversely with mass and increases proportionally with both the observation time and magnetic field strength. Very low pressures (10^{-8}-10^{-9} torr) are required for the signal to be monitored over long periods of time in order to obtain the highest resolution, which is often achieved *via* complicated systems of differential pumping.

Experimental setup. All ESI experiments were carried out using a Bruker BioAPEX^{TM} external source FTICR spectrometer equipped with a horizontal room-temperature, 15 cm inside diameter, 7 T superconducting magnet, an external source, and a 170 mm^3 cylindrical RF-shimmed Infinity^{TM} analyzer cell [91OMS514]. A schematic diagram of the instrument*, outlining the major components, is shown on Figure 2-1. Problems associated with the installation of the nominal 7 Tesla magnet during these studies resulted in using the magnet energized to lower magnetic field. The study of doubly charged cations (Chapter 2) was performed using a 7T magnet, which was a very important feature, since good resolution was required for detecting the doubly charged ions and identifying the observed clusters with the chlorine counter ions (see Figure 2-3b in Chapter 2). The radical merostabilization study (Chapter 4), and the investigation of sulfonium salts (Chapter 5), were performed using a 4.7 T magnet. For the "cation tagging" project (Chapter 3), the magnet was energized to 5.3 T. The resolution achieved in all cases was sufficient for the correct identification and detection of the fragment ions.

The Bruker FTICR external source design has two stages of differential pumping which produces a pressure differential of up to 10^5 between the external source and analyzer regions. The high and ultra-high vacuum regions were maintained using cryopumps (Edwards High Vacuum Co., Woburn, MA). An 800 L/s cryopump (N_2) was used to pump the high gas load region of the external source vacuum compartment where ions exiting the ESI source were accelerated toward the mass analyzer using a series of electrostatic optics. A 400 L/s cryopump evacuated the region between the first and second conductance limits that contained the electrostatic ion transfer optics. An additional 400 L/s cryopump was used to maintain the ultra-high vacuum in the analyzer region.

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* The schematic diagram was drawn by Dr. Clifford H. Watson.

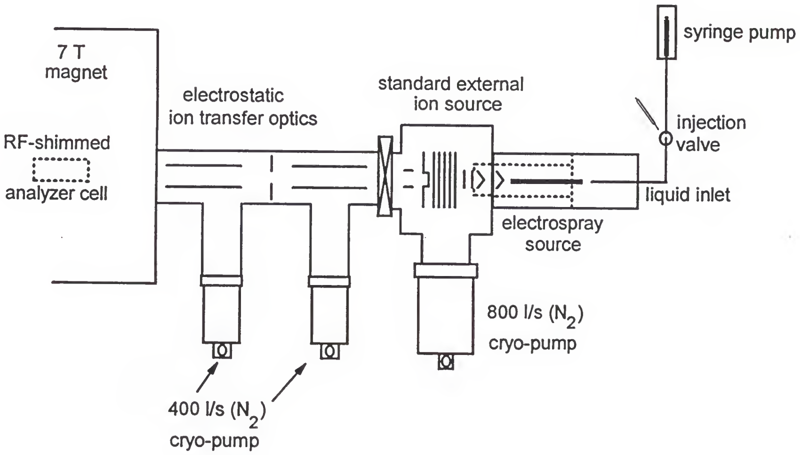


Figure 1-1. Schematic Diagram of ESI FTICR/MS Instrument

After exiting the high pressure ESI source and entering the electrostatic ion optics, ions were accelerated to 2.5-3 kV and tightly focused through the two conductance limits before being accumulated and trapped in the FTICR analyzer cell [91MI1]. Since the ions were continuously produced by the ESI source a set of x-, y-deflection plates were gated "open" during the ion accumulation period for 50 to 200 ms to allow time for ions to accumulate in the analyzer cell. For mass analysis the trapped ions were resonantly excited using a swept frequency RF "chirp" and detected using the broadband detection mode covering a mass range from 50 to 5000 amu. Typically, 25 individual transients were co-added to achieve a suitable signal-to-noise ratio (> 100:1). The raw time-domain transients were apodized [89AS599] and zero-filled [73JMR9, 79AC2198] three times prior to Fourier transformation. The improvement achieved by zero-filling is clearly demonstrated in Figures 1-2 and 1-3, showing plots of data (kinetic energy center-of-mass *vs.* percent fragmentation) before and after zero-filling, respectively. The advantages of the use of zero-filling techniques for peak intensity quantitation have been described in detail elsewhere [97MI1].

The experimental event sequence for obtaining ESI/FTICR mass spectra began with a quench pulse (typically of 10-50 ms duration) to remove any ions remaining in the cell from a previous measurement cycle. After the quench pulse, an ion accumulation event followed (10 - 100 ms) to allow accumulation of ions in the analyzer cell. Precursor ions were isolated using a series of swept-frequency ejection pulses of *ca.* 100 to 300 μs duration to eject all other ions. For the study of doubly charged cations, argon collision gas was introduced *via* a leak valve to a static pressure of $5x10^{-8}$ torr (as indicated on the ion gauge). For the rest of the CAD studies, a pulsed valve introduced the argon collision gas prior to ion activation. With the pulsed valve open for 50 μs, a peak pressure of *ca.* $3x10^{-7}$ mbar was obtained. The precursor ions were excited using a variable amplitude on-resonance excitation pulse of 100 μs duration with RF amplitudes ranging from 50 to 250 V_{p-p} (peak-to-peak) to study the energy dependence of the collisionally activated

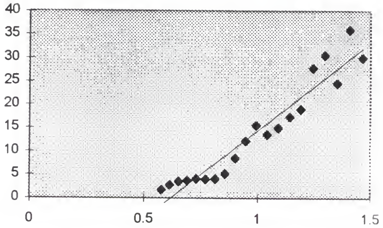


Figure 1-2. Data (Center-of-Mass Kinetic Energy vs. Percent Fragmentation) before zero-filling

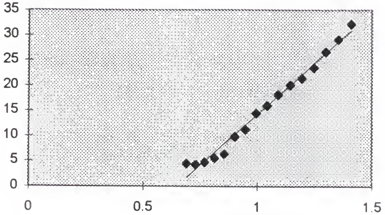


Figure 1-3. Data (Center-of-Mass Kinetic Energy vs. Percent Fragmentation) after zero-filling

dissociation process. Various delay times following the precursor ion's excitation allowed time for the translationally excited precursor ion to undergo collisions and fragment prior to the excitation/detection events. A schematic diagram of the pulse sequences used is shown in Figure 1-4.

To study the dependency of the rate of the parent ion fragmentation on the experimental conditions, the CAD reactions were performed at different delay times and pressures. The delay times following the precursor ion's excitation were varied from 0.05 sec to 3 sec. The effect of an additional delay time before pulsing argon, allowing the ions to cool down, was also studied. For the cation tagging study, in addition to using a pulse valve, some experiments were performed using a leak valve to selectively vary the pressure. Experiments were repeated at pressures from $1\text{x}10^{-9}$ to $1\text{x}10^{-7}$ torr to monitor the extent and rate of fragmentation.

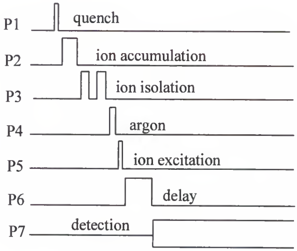


Figure 1-4. Pulse Sequence for Collisionally Activation Dissociation Reactions.

All compounds used in our studies were either commercially available or synthesized in our laboratories following known procedures. The ESI samples were dissolved in 49/49/2 water/methanol/acetic acid solution at a concentration of 0.1 mg/mL and were introduced into the ESI source at a flow rate of 1 μl/min. Different sample concentrations were originally prepared (from 0.01 to 1 mg/ml) but it was found that 0.1 mg/mL sample concentration provided the optimal signal.

1.3. Investigation of Various Salts by ESI FTICR/MS - Aims and Objectives

Electrospray ionization coupled with FTICR mass spectrometry provides an excellent method for studying gas phase reactions. Monitoring gas phase reactions using mass spectrometry is a fast and relatively easy approach. One big advantage, as compared to studying similar systems in liquid phase, is the absence of solvent effects. For simplification, singly and multiply charged organic salts that can be readily electrosprayed and analyzed *via* mass spectrometry were investigated. Pyridinium salts were chosen mainly due to the exceptional stability of the *N*-substituted pyridinium cations, such as Py^+-Me or Py^+-Bz. These cations have been previously studied using mass spectrometry [84JOC764], and they have been shown to undergo little or no fragmentation even under extreme experimental conditions. In previous reports from our laboratory, various pyridinium salts have been studied utilizing laser desorption FTICR/MS [89OMS1017, 90JACS2471, 90JACS2479, 92OMS1317, 94OMS96]. Now these studies have been extended providing the first ESI/MS report [95JMS1581] of doubly charged organic cations that exist as doubly charged salts rather than as cations formed by double protonation. The stability of the *N*-substituted pyridinium cations has been utilized to study "cation tagging" as an easy and convenient way of monitoring gas phase reactions [96JACS1]. Additionally, the still very controversial theory of carbon-radical merostabilization [96JACS11905] has been studied. To show the versatility of the ESI FTICR/MS, gas-phase studies were extended to investigating some singly and multiply charged sulfonium salts. This types of compounds have not yet been studied in much detail, and the mass spectrometry reports that appear in the literature are limited. Utilizing the approaches used for studying pyridinium salts, the effect of the substituent groups on the fragmentation patterns of sulfonium salts was investigated, dissociation reaction pathways were studied and ion/molecule reaction mechanisms were identified [97IJMSIPr].

1.3.1. Investigation of Doubly Charged Pyridinium Salts by ESI FTICR/MS

Doubly charged organic salts are relatively unstable in the gas phase, and the investigation of their chemical fragmentation is not an easy task. Doubly charged cations can easily undergo scission to form more stable and energetically favored singly charged cations. The available literature on mass spectrometric investigations of doubly charged organic salts is still limited. Different approaches with varying success, utilizing a variety of ionization techniques, have been previously reported. However, to the best of our knowledge at the time when this study was completed, there were no reports describing the applications of ESI FTICR/MS for studying doubly charged organic salts. Three doubly charged pyridinium salts were chosen as model compounds to identify their fragmentation patterns, perform ion-molecule reactions and study the propensity towards gas phase S_N1 and S_N2 reaction pathways.

1.3.2. "Cation Tagging" for Studying Pyrolysis of Esters Reactions by ESI FTICR/MS.

There are numerous reactions in organic chemistry that do not involve the formation of charged species and it is, therefore, difficult to study them in the gas phase.

However, if a stable, localized positive charge can be introduced to one end of a system the reaction that occurs at the other end can be monitored, and this should provide a general technique for studying gas phase reactions. Similar approaches have been described by Gross *et al.* [92IJMSIP137, 94ACR361] for "remote-site fragmentation" and by Wilson *et al.* [93JCSCC784, 93JACS8495, 93TL8043, 93JACS10334, 95JACS554, 95TL6846] for the investigation of fullerene chemistry. However, the full potential of the general application of positive "tags", that can be attached to any system, has apparently not yet been realized. Seven different tetraphenylpyridinium esters were chosen as model compounds to show the application of this technique for the calculation of threshold fragmentation energies and determination of rate constants for gas phase pyrolysis reactions using the electrospray FTICR/MS technique. The positive "tag" used in this case is the tetraphenylpyridinium group, which has previously been shown to be extremely stable and to undergo no further fragmentation.

1.3.3. Investigation of Radical Merostabilization by ESI FTICR/MS

It is well known that electron-donating substituents stabilize carbon cations while electron-withdrawing substituents stabilize carbon anions. It was originally proposed by Dewar that this stabilization theory can be extended to carbon-centered radicals, where the additional stabilization would occur when both an electron-donor and an electron-acceptor group are present at the radical site. This effect was described as merostabilization by Katritzky [65MI1, 71MI1, 73H67, 74JCSPT(1)1422, 74JCSPT(1)1427] and, later, as the capto-dative effect by Viehe [78ACIEE691, 79ACIEI917, 85ACR148]. However, there is still much controversy regarding the existence of such stabilization. For this study a new approach for investigating the existence of radical merostabilization in the gas phase by ESI FTICR/MS was taken. Three different 4-(1′-substituted-2′-phenethyl)-1-methylpyridinium salts containing a neutral, an electron-donor or an electron-acceptor group as the α-substituent, respectively, were chosen as model compounds to calculate the threshold fragmentation energies (E_O) as a measurement of stability. If the merostabilization theory is correct, the pyridinium cation, containing both electron-donor and electron-acceptor substituent groups, should have a significantly lower E_O than the analogs containing a neutral or an electron-acceptor substituent.

1.3.4. Gas Phase Investigations of Sulfonium Salts by Electrospray FTICR/MS

Sulfonium salts were chosen in order to extend the detailed investigations of fragmentation patterns and ion-molecule reactions of singly and doubly charged pyridinium cations to another class of organic salts. There is still only a limited number of mass spectrometry reports describing the gas phase behavior and properties of these compounds. Twelve sulfonium salts were chosen and collisionally activated dissociation experiments were performed in addition to various ion-molecule reactions, to investigate dissociation pathways in the gas phase and to study the stabilizing/destabilizing effect of electron donating/withdrawing substituents on the sulfonium ions.

CHAPTER 2

INVESTIGATIONS OF DOUBLY CHARGED ORGANIC CATIONS BY ELECTROSPRAY FTICR/MS

2.1. Introduction

Organic species containing two positive charges are difficult to detect as such in mass spectrometry for the following reasons: (i) they are intrinsically unstable due to intramolecular coulombic repulsion forces and tend to undergo fragmentation with relative ease; (ii) clustering of a doubly charged ion with a counter-ion can easily occur; and (iii) loss or gain of one electron to produce a singly charged species is often favored [94JPOC465]. The limited literature available has described a range of techniques for ionization and detection of doubly charged organic species, including FDMS (field desorption mass spectrometry) [75JOC636, 83AC1310, 88TL3463], SIMS (secondary ionization mass spectrometry) [80AC2054], PDMS (plasma desorption mass spectrometry) [88TL3463], FABMS (fast atom bombardment mass spectrometry) [87JACS1980, 93OMS71, 95JMS282], LDMS (laser desorption mass spectrometry) [84AC866], and EHMS (electrohydrodynamic mass spectrometry) [83IJMSIP135]. The types of organic compounds previously studied as doubly charged organic salts by these techniques include bisphosphonium halides [75JOC636, 87JACS1980, 93OMS71] and diquaternary ammonium salts [80AC2054, 83AC1310, 84AC866, 89IJMSIPr139].

This study describes the generation of doubly charged organic ions using a previously unreported approach -- ESI (electrospray ionization) coupled with FTICR/MS(Fourier Transform Ion Cyclotron Resonance Mass Spectrometry).

Although a study of multiply charged polyethylene glycol coordinated Na^+ and K^+ cations (MW = 200–17500) by ESIMS had been reported [88JPC546], at the time when this study was performed, no other reports of ESIMS studies of organic compounds that exist as doubly charged salts rather than as cations formed by double protonation were found.

Dipyridinium compounds were chosen for this investigation. Previous FTICR/MS studies from this laboratory of singly charged pyridinium cations have clarified processes occurring in the gas phase [89OMS1017, 90JACS2471, 92OMS1317, 94OMS96] and illustrated mechanisms in solution [90CSR83]. These earlier reports included investigation of novel fragmentation pathways of pyridinium monocations using collisionally activated dissociation (CAD) and ion-molecule reactions in pyridine-toluene mixtures. With the present work, using electrospray mass spectrometry, we have extended these studies to doubly charged pyridinium cations. The compounds investigated were *N*-benzyl-2,4-diphenyl-6-[(*N*-methyl)-3-pyridinium] pyridinium diperchlorate **(2-1)**, *N*-[α-(4-*N,N*-dimethylaminopyridinium)benzyl]-4-dimethylaminopyridinium ditetrafluoroborate **(2-2)** and *N*-benzyl-2,6-diphenyl-4-(*N*-methyl-4-pyridinium)pyridinium ditetrafluoroborate **(2-3)** as shown on Figure 2-1.

2.2 Results and Discussion

Compound **(2-1)** (MW 613), (Figure 2-2) displayed major peaks at (i) *m/z* 1125, *m/z* 1127 and *m/z* 1129 plus minor isotopes at *m/z* 1126, *m/z* 1128 and *m/z* 1130, respectively, corresponding to the cluster $[2CAT^{++}3AN^{-}]$, where the counter ion can be

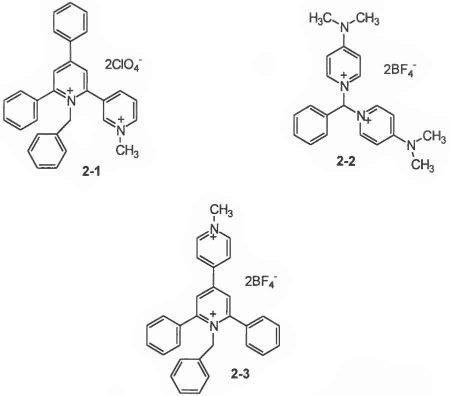


Figure 2-1. Model Compounds Chosen for the Investigation of Doubly Charged Cations by Electrospray Fourier Transform Ion Cyclotron Resonance Mass Spectrometry

either $^{35}ClO_4^-$ or $^{37}ClO_4^-$, (ii) at *m/z* 513 and *m/z* 515 corresponding to the cluster $[CAT^{++}AN^-]$, where the counter ion again can be either $^{35}ClO_4^-$ or $^{37}ClO_4^-$, (iii) at *m/z* 207, corresponding to the doubly charged ion, (iv) at *m/z* 413 generated *via* loss of a proton from the doubly charged ion or *via* loss of HAN from the ion at *m/z* 513, and (v) at *m/z* 323 generated *via* loss of a benzyl group from the doubly charged ion. The peak corresponding to the doubly charged cation at *m/z* 207 ($z = 2$) was observed in the broad band spectra with a relative intensity of 50% (the highest intensity of a doubly charged cation so far observed by us), from which we were able to obtain a CAD spectrum (Figure 2-2).

Additional fragment peaks were observed (vi) at *m/z* 398 (20%) and (vii) at *m/z* 171 (6%). The peak at *m/z* 398 $[CAT^{++} - H^+ - {}^{\bullet}CH_3]$ corresponds to the loss of a methyl radical from the ion at *m/z* 413 $[CAT^{++} – H^+]$. The peak at *m/z* 171 corresponds to the loss of two C_6H_4 molecules from the ion at *m/z* 323 (100%).

CAD experiments were also performed for the ions with *m/z* 513 (40%) $[CAT^{++}AN^–]$, *m/z* 413 (10%) $[CAT^{++} – H^+]$, *m/z* 323 and *m/z* 207 $[CAT^{++}]$ (see Figure 2-2). The CAD spectrum of the ion at *m/z* 513 showed formation of the ions at *m/z* 413 and a very strong signal for the ion at *m/z* 323, which supports the stable structure assigned in Figure 2-2. This stability was confirmed when CAD was performed on the ion at *m/z* 323: the only signal observed was a weak signal from a fragment ion at *m/z* 171, which we believe is formed by the elimination of two molecules of benzyne C_6H_4 from the ion at *m/z* 323.

The CAD spectrum of the ion at *m/z* 413 showed formation of the fragment ion at *m/z* 398, but no signal from the ion at *m/z* 323. We suggest that after loss of a proton from the CH_2 group, a C–C bridge is formed between the CH^- and the pyridinium group to stabilize the structure at *m/z* 413 $[CAT^{++} – H^+]$. This nicely explains further loss of a methyl radical (presumably followed by a hydrogen rearrangement to give *m/z* 398) and the absence of other product ions. Alternatively, the ion at *m/z* 413 could be generated *via* loss of a HAN molecule from the cluster ion at *m/z* 513.

The CAD spectrum of the doubly charged cation at *m/z* 207 showed the loss of benzyl cation to form the stable fragment ion at *m/z* 323: loss of a benzyl group is expected to be favored over the loss of a methyl group.

Figure 2-2 shows the overall fragmentation patterns of compound (**2-1**) and its product peaks as observed in the broad band spectrum as well as in the CAD spectra. The relative intensity of the ions detected was found to be concentration dependent, as can be seen in Figures 2-3 and 2-4. Figure 2-3a shows the broad band spectrum of compound (**2-1**) at a sample concentration of 0.3 mg/mL. At this concentration the peaks at *m/z* 1125-1130 corresponding to the cluster [$2CAT^{++}3AN^{-}$] can be observed (Figure 2-3b). The base peak corresponds to the ion at *m/z* 513 [$CAT^{++}AN^{-}$] (Figure 2-3c) and the doubly charged ion at *m/z* 207 was observed with a relative intensity of 20%. Figure 2-4a shows the broad band spectrum of compound (**2-1**) at sample concentration of 0.1 mg/ml. At this lower concentration, the cluster [$2CAT^{++}3AN^{-}$] was not observed, but the doubly charged ion at *m/z* 207 (Figure 2-4b) was observed with a relative intensity of 50%, and the base peak was found to correspond to the ion at *m/z* 323 [CAT^{++}- $C_7H_7^{+}$] (Figure 2-4c).

Compound (**2-2**) (MW 508), (Scheme 2-5) displayed five major peaks in its mass spectrum. The first was a peak at *m/z* 421 (42%) corresponding to the cluster ion composed of the dication and one tetrafluoroborate anion [$CAT^{++}AN^{-}$]. In addition, the dication itself was observed at *m/z* 167 (10%) [CAT^{++}, $z = 2$], with fragments at *m/z* 333 (90%) [$CAT^{++} - H^{+}$] and *m/z* 211 (100%) [$CAT^{++} - C_7H_{11}N_2^{+}$]. The last peak was observed at *m/z* 197 (16%) corresponding to [$CAT^{++} - C_8H_{13}N_2^{+}$] (Scheme 2-5). The most abundant ions were isolated and further subjected to CAD studies, to help in the identification of the structures of the fragment ions.

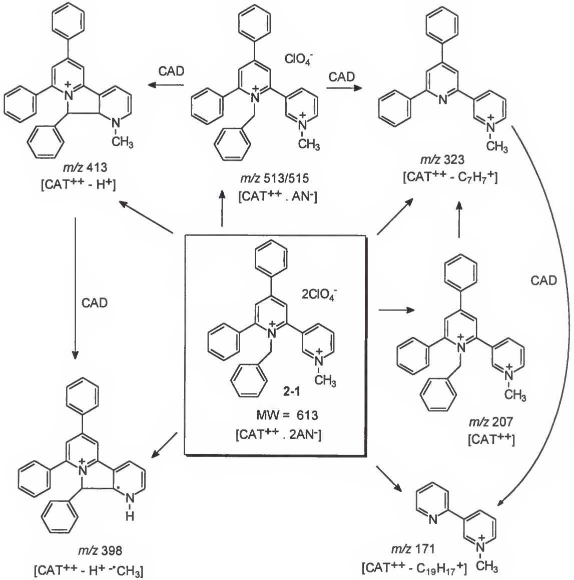
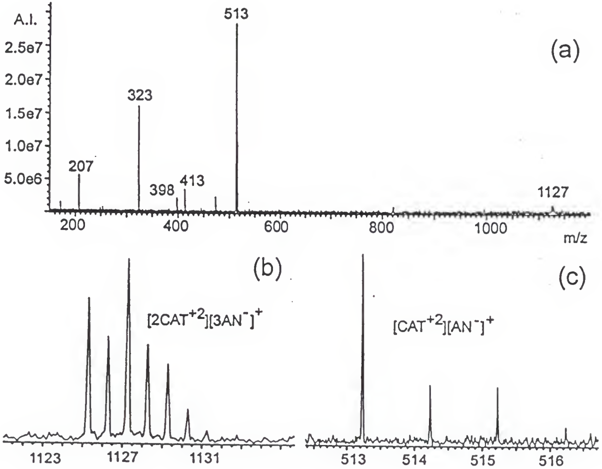
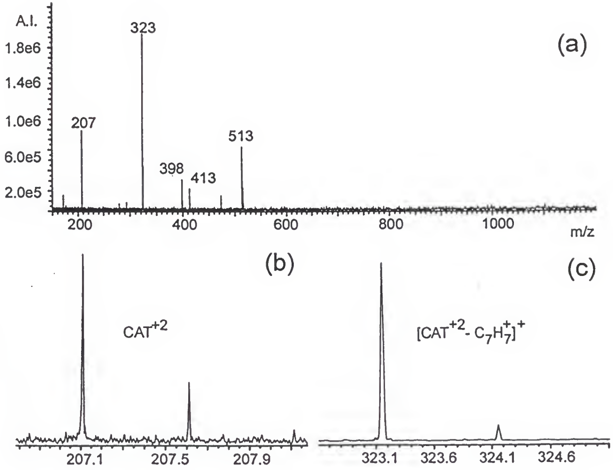


Figure 2-2. Fragmentation Pattern for Compound **2-1**.



Figures 2-3a, 2-3b, and 2-3c. Electrospray Mass Spectra of Compounds **2-1** at a Sample Concentration of 0.2 mg/mL. (a) Broad-band Spectrum; (b) Peaks at *m/z* 1125-1130, corresponding to $[2CAT^{2+}\bullet 3AN^{-}]^{+}$; (c) Base Peak at *m/z* 513, corresponding to $[CAT^{2+}\bullet AN^{-}]^{+}$



Figures 2-4a, 2-4b, and 2-4c. Electrospray Mass Spectra of Compounds **2-1** at a Sample Concentration of 0.1 mg/mL. (a) Broad-band Spectrum; (b) Peak at *m/z* 207, corresponding to [2CAT^{2+}]; (c) Base Peak at *m/z* 323, corresponding to [CAT^{2+} - $C_7H_7^+$]$^+$

Collision activated dissociation (CAD) experiments using neutral argon as the collision gas were performed on the ions at *m/z* 421, *m/z* 333 and *m/z* 211. To obtain the best possible spectra, different delay times were used to optimize the number of collisions and enhance the dissociation yield. The dependence of results on the delay time is highlighted in Table 2-1.

Table 2-1. CAD of ions at *m/z* 421, *m/z* 333 and *m/z* 211. The calculated collisional energy, using argon as a target molecule, was varied over a range of 1 - 10 eV.

	Ion *m/z* 421	Ion *m/z* 333	Ion *m/z* 211
Delay Time (s)	Peaks Observed [*m/z*, (relative intensity)]		
0	421(100%)	333(100%)	211(100%)
0.25	333(100%), 211(30%)	333(100%), 211(30%)	197(100%)
0.5	333(100%), 211(40%)	333(100%), 211(30%)	–
1.0	333(100%), 211(30%),	–	–

The strong peak at *m/z* 333 is probably due to loss of the acidic proton at the bridging CH by the CAT^{++}; analogous behavior is known in solution [94MI1]. This ion next loses a molecule of 4-dimethylpyridine (DMAP) to generate the peak at *m/z* 211 with cyclization and hydrogen rearrangement. The peak at *m/z* 197 was presumably generated *via* loss of a methylene group from the ion at *m/z* 211. CAD of the doubly

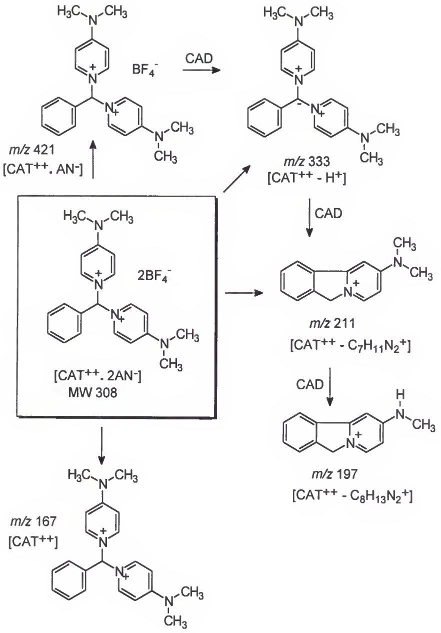


Figure 2-5. Fragmentation Patterns for Compound **2-2**.

charged ion itself (*m/z* 167) was not obtained due to its very weak signal. Scheme 2-5 shows the fragmentation patterns of compound **(2-2)** and its product peaks, as observed in the broad band spectrum as well as in the CAD spectra.

Compound **(3-3)** (Figure 2-6) displayed two major peaks at *m/z* 399 (80%) and *m/z* 323 (100%). The peak at *m/z* 399 corresponds to loss of a methyl cation from the doubly charged cation at *m/z* 207, and the peak at *m/z* 323 corresponds to loss of a benzyl cation from the ion at *m/z* 207, forming in both cases the corresponding stable singly charged structures. In this case again, the loss of a benzyl cation was favored over loss of methyl cation which accounts for the higher intensity of the peak at *m/z* 323 corresponding to [CAT^{++} - $C_7H_7^+$]. The doubly charged cation at *m/z* 207 was observed with relative intensity of 30%. Compound **(2-3)** displayed one further fragment ion at *m/z* 309 (10%), corresponding to either the loss of CH_2 and $C_6H_5CH_2^+$ or to the loss of CH_3^+ and C_6H_5CH groups.

CAD experiments were performed on each of the ions observed. When the ion at *m/z* 399 collided with argon atoms, the only fragment ion observed was *m/z* 91, most likely a tropylium ion. Presumably a neutral molecule of 2,6-diphenyl-4-dipyridine **(2-4)** is also formed in this dissociation (see Figure 2-6). The fragmentation pathway for generating compound **(2-4)** was expected because in this manner a stable neutral molecule was formed, which is an energetically favored pathway. No fragment peaks were observed when the ions at *m/z* 323 and *m/z* 309 were collided with neutral argon. The CAD of the doubly charged ion led to further formation of the ions at *m/z* 399 and *m/z* 323.

Additionally, the doubly charged cations of compounds **(2-1)** and **(2-3)** were isolated and further studied by "reactive" collisional activation. The precursor ions were translationally excited with a relatively low amplitude RF pulse (typically 80V with a 30 ms pulse width) and allowed to interact with a "reactive" neutral. Without the RF pulse there were no ion/molecule reactions observed. Instead of neutral argon

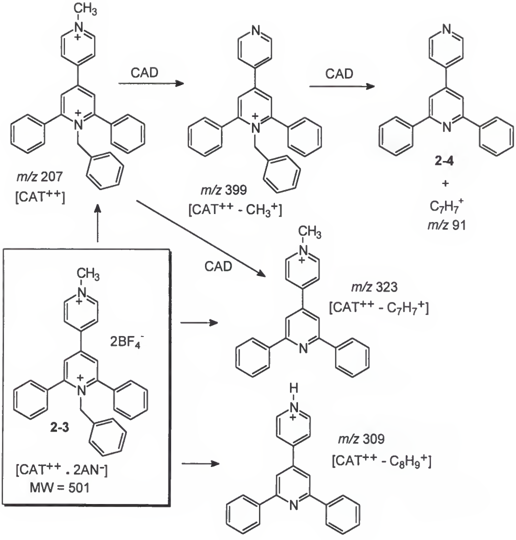


Figure 2-6. Fragmentaion Pattern for Compound **2-3**.

being introduced through the leak valve, we introduced 4-dimethylpyridine (DMAP) at pressure of 1 x 10^{-7} torr (uncorrected ion gauge reading), to monitor possible transfer of a methyl or benzyl group from the doubly charged cations to the DMAP molecules. The reactions were monitored for different reaction delay times.

When the translationally excited, doubly charged cation of compound (**2-1**) was reacted with DMAP, four peaks were observed - *m/z* 323, corresponding to loss of benzyl cation [CAT^{++} - $C_7H_7^+$], *m/z* 213, corresponding to DMAP plus $C_7H_7^+$ [DMAP + $C_7H_7^+$], *m/z* 123, corresponding to a protonated DMAP molecule [DMAP + H^+] and *m/z* 91, corresponding to the tropylium ion [$C_7H_7^+$], Figure 2-7.

The doubly charged cation of compound (**2-3**) was reacted with DMAP to produce peaks at (i) *m/z* 323, corresponding to loss of benzyl [CAT^{++} - $C_7H_7^+$], (ii) *m/z* 245, corresponding to two DMAP molecules attached *via* a proton bridge [2DMAP + H^+], (iii) *m/z* 213, corresponding to DMAP plus benzyl [DMAP + $C_7H_7^+$], (iv) *m/z* 123, corresponding to protonated DMAP [DMAP + H^+] and *m/z* 91, corresponding to the tropylium ion [$C_7H_7^+$] as shown in Scheme 2-7.

To investigate the mechanism of the benzyl transfers observed, *i.e.*, as to whether they follow a S_N1 or a S_N2 pathway, the benzyl ions were continually ejected from the analyzer cell during the reaction period for both compounds (**2-1**) and (**2-3**). The only ions then observed in the spectrum of both compounds were *m/z* 323 [CAT^{++} - $C_7H_7^+$], *m/z* 245 [2DMAP + H^+] and *m/z* 123 [DMAP + H^+]. The hydrogen cation probably arises from deprotonation of compounds (**2-1**) and (**2-3**). No ion at *m/z* 213, corresponding to DMAP plus benzyl [DMAP + $C_7H_7^+$] was observed in either experiment. This shows that the benzyl transfer occurs *via* free benzyl cation, *i.e.*, *via* a S_N1 reaction pathway. This result confirmed our previous investigations of similar reaction mechanisms in the gas phase [90JACS2471]. Ion-molecule reactions are discussed in general in Chapter 5 of this thesis.

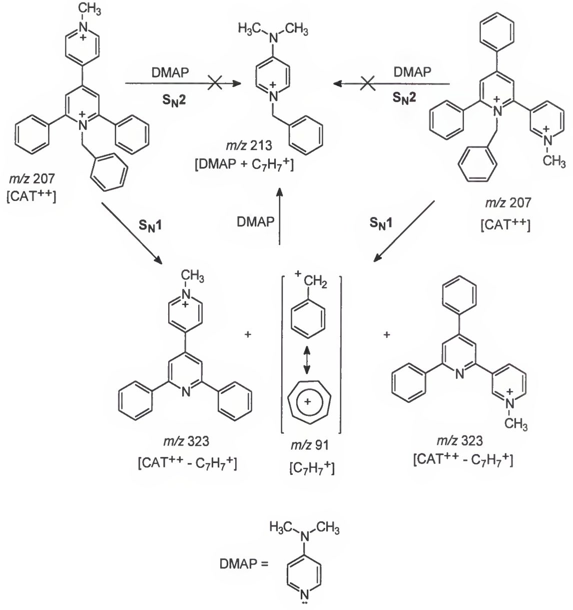


Figure 2-7. Collisionally Activated Dissociation Spectra of the Doubly Charged Cations of Compounds **2-1** and **2-3**.

2.3 Summary and Conclusions

Previously reports from this group included collisionally activated dissociation studies which gave rise to unimolecular reactions [90JACS2471, 89OMS1017] and bimolecular reactions [94OMS96] of various pyridinium systems. Now this study was extended to doubly charged pyridinium cations, whose behavior had not been previously studied in detail due to problems associated with their production and detection in the gas phase.

Common trends observed in the fragmentation pattern of all three doubly charged compounds studied are formation of a cluster of the type [$CAT^{++}.AN^{-}$]; favored loss of a positively charged species, such as hydrogen, methyl or benzyl ions, forming in this way stable singly charged cations; and observation of the doubly charged cations in relatively high intensities. Ion/molecule reactions of doubly charged pyridinium cations that lead to the transfer of a benzyl group were used for investigating the propensity towards gas phase S_N1 and S_N2 reaction pathways. In this series, S_N1 type reactions in gas phase were detected exclusively.

These results demonstrate that ESIMS is a powerful technique for detection of organic salts which normally exist as doubly charged cations. The FTICR instrumentation provides an excellent method to study the behavior of doubly charged systems in the gas phase due to its high resolution, MS/MS, and long trapping capabilities.

CHAPTER 3

"CATION TAGGING" FOR STUDYING PYROLYSIS REACTIONS OF ESTERS BY ELECTROSPRAY FTICR/MS

3.1. Introduction

The concept of remote-site fragmentation was first developed as a useful technique by mass spectrometrists in the early 1980's [83JACS5487, 85BMS95, 85JACS1863], although some examples can be found in literature prior to that [70OMS1035], [77OMS387, 77OMS541]. The method, mechanism and applications of remote-site fragmentation have since been studied extensively, especially by Gross [92IJMSIP137, 94ACR361] and Adams [90MSR141]. The ion fragmentations are called "remote-site" or "charge-remote" because the ion decompositions occur at a site in the ion that is spatially separated from the charge site. The charge site is stable and localized and does not play any significant role in the fragmentation process. Most applications of remote-site fragmentation discussed in the literature to date have involved structural analysis of various biomolecules [83JACS5487, 85JACS1863], surfactants [89BEMS89], organic dyes [94OMS631], and other lipophilic material [92IJMSIP137]. Remote-site fragmentation reactions have been studied for a variety of alkali-metal-cationized fatty acids [94AC861, 87AC1576] and alcohols [86JACS6915], alkyltriphenylphosphonium salts [85AC1181], steroid conjugates and bile salts [89BEMS89], carboxylate anions of unsaturated fatty acids [85JACS1863], and protonated pyridines [88RCMS214]. Remote-site elimination of aldehydes and water was also observed [89JACS435]. Remote-site fragmentation spectra have been reported for both cations and anions; however most structures discussed have contained a long alkyl chain where the fragmentation occurred.

Clearly, it should be possible to extend the concept of "charge-remote" fragmentation into a general method for the study of gas phase reactions by introducing a stable and localized positive charge at one end of a system, so that a reaction which occurs at the other end, can be monitored. To our knowledge, the only previous reports of such "cation tagging" are by Wilson and his co-workers [93JCSCC784, 93JACS8495, 93TL8043, 93JACS10334, 95JACS554, 95TL6846] who attached a crown-ether-coordinated potassium cation to C_{60} derivatives and used the technique to study a number of fullerene reactions. The technique of "cation tagging" should be generally applicable to the gas phase study of organic reaction mechanisms, which do not normally involve charged species, and in this study the use of substituted *N*-arylpyridinium salts for such general applications is proposed. *N*-Arylpyridinium cations have been shown to be very stable in the gas phase [84JOC764]. The scope of the technique is illustrated in the present work by a study of ester pyrolysis using tetraphenylpyridinium with a remote ester group. Thermal decomposition reactions were found to take place as expected at the ester group, rather that at the charged pyridinium moiety, to form the corresponding charged acids and neutral olefins. The pyrolysis of esters has been extensively studied both in solution [60CR431] and in the gas phase [79MI1, 75JCSPT(2)1025, 78JCSPT(2)1090, 71PPOC75, 83JCSPT(2)1875, 84JCSPT(2)647, 87JCSPT(2)1683]. Gas phase rates of formation of the corresponding alkenes were measured and the effects of different substituents were extensively studied [75JCSPT(2)1025, 78JCSPT(2)1090, 71PPOC75], [83JCSPT(2)1875, 84JCSPT(2)647, 87JCSPT(2)1683]. However, no reports of the investigation of ester pyrolysis utilizing mass spectrometry were found.

3.2. Results and Discussion

3.2.1. Synthesis and Characterization of the Eight Alkoxycarbonyl Substituted Pyridinium Salts Chosen as Model Compounds

Eight novel pyridinium salts (**3-3a-f**) were prepared for this study by Dr. Ming Qi. as shown on Figure 3-1, using methods previously described in the literature [80T679, 84AGE420]. Amines **3-2d,e,f,** that were not commercially available, were also prepared by Dr. Ming Qi *via* catalyzed hydrogenation of the appropriate nitro compounds [86JOC3903]. For proper characterization of these salts I obtained high resolution spectra using the FTICR mass spectrometer. The data is summarized in Table 3-1.

3.2.2. CAD Study of the Pyrolysis Reactions of Esters.

Seven 1,2,4,6-tetraphenylpyridinium esters with different CO_2R substituents in the 1-phenyl group (**3-3a** - **3-3g**) (Table 3-1) were subjected to CAD experiments in the gas phase. The products obtained in each case were the acids **3-5a** and **3-5b** and the corresponding neutral alkenes **3-6a** - **3-6g** (Figure 3-2). The reactions proceed *via* six-membered cyclic transitions states (**3-4a** - **3-4g**) described in the literature [75JCSPT(2)1025, 78JCSPT(2)1090, 83JCSPT(2)1875, 92MI1]. Formation of neutral olefins *via* CAD reactions has been previously observed [90JACS2479]. For studying the possible influence of the counter ion, compounds **3-3a** and **3-3h** were synthesized to have the same cations but different anions. The CAD spectra of both compounds were investigated and the counter ion was found to have no significant influence, which confirms our previous reports (Chapter 2 of this thesis).

For each substrate studied, two major peaks were observed: (i) the parent peak from the corresponding compounds **3-3a** - **3-3g** and (ii) the fragment ion peak at *m/z* 429, corresponding to the acids **3-5a** and **3-5b** (Figure 3-2). The two peaks were detected in different relative intensities as the amplitude of the RF pulse used to excite the parent ion was varied. Data were collected from 100% relative intensity (RI) of the parent ion and 0% RI of the fragment ion to 0% RI of the parent ion and 100% RI of the fragment ion. Figures 3-3 to 3-7 show the change of the relative intensities of parent and fragment peaks with increase of the RF excitation pulse for compounds **3-3a** and **3-3f**, respectively. The translational energy imparted to an ion during the excitation stage of the FTICR CAD process was calculated using equation 3-1 [82AC96, 86IJMSIP93], where q is the ionic charge, V is the peak-to-peak amplitude of the RF excitation pulse ($V_{p\text{-}p}$), t is the RF pulse width, m is the ionic mass, and d is the distance between the excitation plates of the analyzer cell.

$$E_{ion} = \frac{q^2 V^2 t^2}{8md^2} \qquad (3\text{-}1)$$

$$E_{cm} = E_{ion}\frac{M_{Ar}}{M_{Ar} + m} \qquad (3\text{-}2)$$

The nominal center-of-mass collision energy (E_{cm}) can be calculated from equation 3-2, as described previously [90JACS2471], where M_{Ar} is the mass of the neutral collision gas (Ar) and m is the ionic mass. In previous studies from this laboratory [90JACS2479],

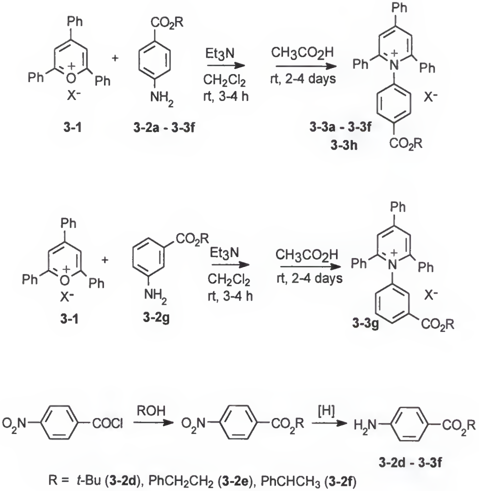


Figure 3-1. Synthesis of Alkoxycarbonyl Substituted Pyridinium Salts. R = CH_2CH_3 (**3-3a**); $(CH_2)_2CH_3$ (**3-3b**); $CH(CH_3)_2$ (**3-3c**); $C(CH_3)_3$ (**3-3d**); $(CH_2)_2Ph$ (**3-3e**); $CH(Ph)CH_3$ (**3-3f**); CH_2CH_3 (**3-3g**); CH_2CH_3 (**3-3h**).

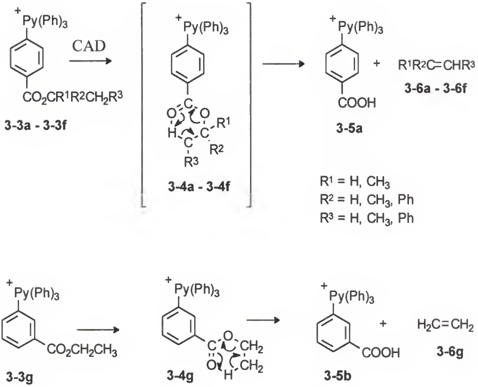
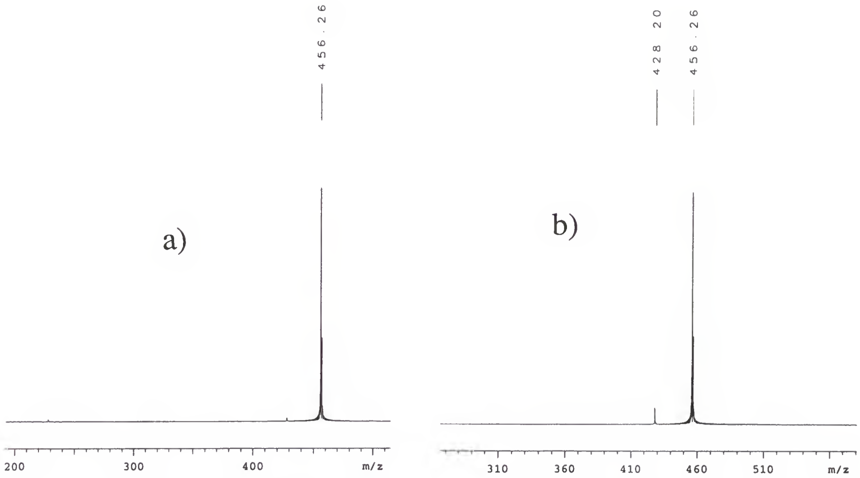


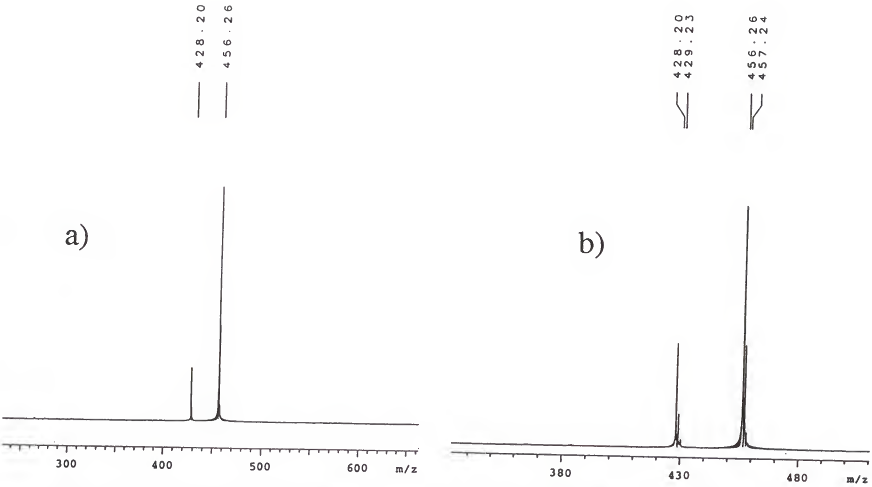
Figure 3-2. Fragmentation Pattern for Compounds **3-3a** - **3-3f** and Reaction Mechanisms

No	substituent	X^-	yield	M^+(exp)	M^+(calc)	Δ ppm
3-3a	*p*-$CO_2CH_2CH_3$	ClO_4^-	90%	456.1946	456.1964	3.95
3-3b	*p*-$CO_2(CH_2)_2CH_3$	ClO_4^-	85%	470.2099	470.2120	4.47
3-3c	*p*-$CO_2CH(CH_3)_2$	ClO_4^-	93%	470.2102	470.2120	3.83
3-3d	*p*-$CO_2C(CH_3)_3$	BF_4^-	75%	484.2293	484.2277	3.30
3-3e	*p*-$CO_2(CH_2)_2Ph$	BF_4-	90%	532.2281	532.2276	0.94
3-3f	*p*-$CO_2CH(Ph)CH_3$	BF_4^-	84%	532.2270	532.2276	1.13
3-3g	*m*-$CO_2CH_2CH_3$	ClO_4^-	90%	456.1967	456.1964	0.66
3-3h	*p*-$CO_2CH_2CH_3$	BF_4^-	85%	-	-	-

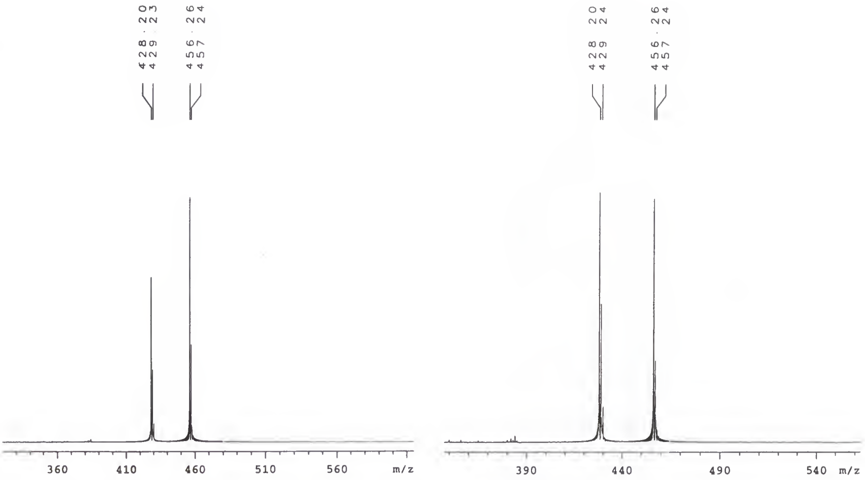
Table 3-1. Reaction Yields and High resolution Mass Spectrometry Data for Pyridinium Salts **3-3a - 3-3h**



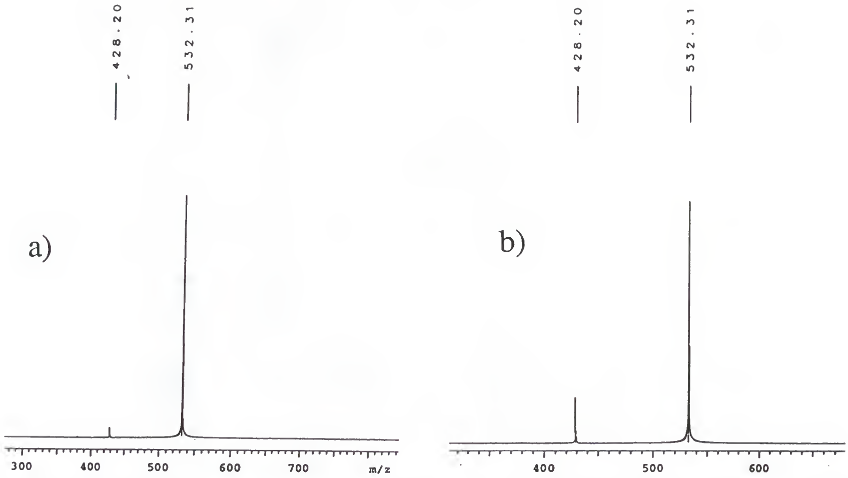
Figures 3-3a and 3-3b. ESI CAD Mass Spectra of Compound **3-3a**. (a) V = 5V, Intensity of Parent Ion (*m/z* 456.26) = 100%; Intensity of Fragment Ion (*m/z* 428.20) *ca.* 1%. (b) V = 8V, Intensity of Parent Ion (*m/z* 456.26) = 100%; Intensity of Fragment Ion (*m/z* 428.20) *ca.* 7%.



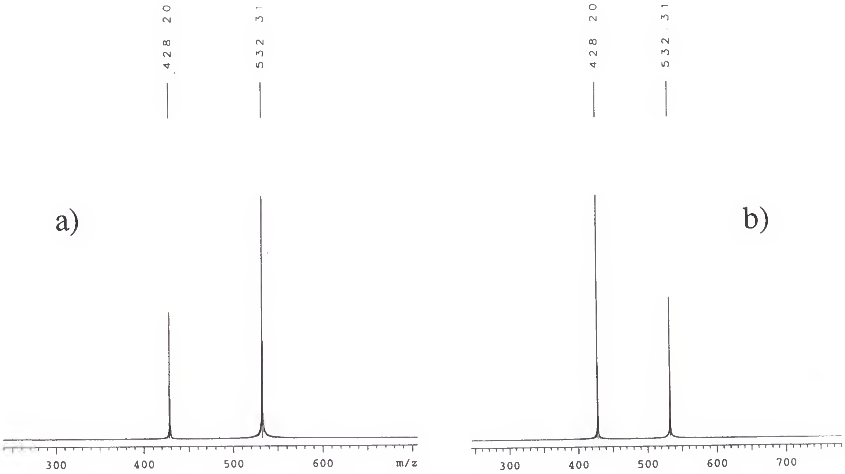
Figures 3-4a and 3-4b. ESI CAD Mass Spectra of Compound **3-3a**. (a) $V = 9.5$V, Intensity of Parent Ion (*m/z* 456.26) = 100%; Intensity of Fragment Ion (*m/z* 428.20) *ca*. 22%. (b) $V = 16$V, Intensity of Parent Ion (*m/z* 456.26) = 100%; Intensity of Fragment Ion (*m/z* 428.20) *ca*. 43%.



Figures 3-5a and 3-5b. ESI CAD Mass Spectra of Compound **3-3a**. (a) $V = 19$V, Intensity of Parent Ion (*m/z* 456.26) = 100%; Intensity of Fragment Ion (*m/z* 428.20) *ca*. 67%. (b) $V = 21$V, Intensity of Parent Ion (*m/z* 456.26) *ca*. 97%; Intensity of Fragment Ion (*m/z* 428.20) = 100%.



Figures 3-6a and 3-6b. ESI CAD Mass Spectra of Compound **3-3f**. (a) $V = 6$V, Intensity of Parent Ion (*m/z* 532.31) = 100%; Intensity of Fragment Ion (*m/z* 428.20) *ca*. 4%. (b) $V = 9.5$V, Intensity of Parent Ion (*m/z* 456.26) = 100%; Intensity of Fragment Ion (*m/z* 428.20) *ca*. 19%.



Figures 3-7a and 3-7b. ESI CAD Mass Spectra of Compound **3-3f**. (a) $V = 12\text{V}$, Intensity of Parent Ion (*m/z* 532.31) = 100%; Intensity of Fragment Ion (*m/z* 428.20) *ca*. 53%. (b) $V = 15\text{V}$, Intensity of Parent Ion (*m/z* 456.26) *ca*. 58%; Intensity of Fragment Ion (*m/z* 428.20) = 100%.

[90JACS2471, 92OMS1317, 90JCSPT(2)1051, 94OMS96], the nominal center-of-mass energy was plotted *vs* percentage of fragmentation ($\Sigma F+/\{[P+] + [\Sigma F+]\}$) and the straight line portions of these plots were extrapolated to zero fragmentation to give the observed threshold energy (E_o).

In the present study we used the "CRUNCH" program for analysis of ion/molecule reaction cross sections, written by P. B. Armentrout and K. M. Ervin [85JCP83]. The fitting function in that program was modified slightly to be more appropriate to FTICR CAD conditions as shown in equation 3-3, where k is the CAD rate constant, k_o is an energy-independent scaling factor, E_o is the threshold energy and v is treated as a variable parameter. This form has been predicted for CAD processes and Armentrout *et al.* have proved experimentally that it provides accurate CAD thresholds [86JPC5135]. The CAD rate constant (k) is derived from the percent fragmentation observed (equation 3-4), where (I / I_o) is the fragmentation ratio observed, n is the number density of the collision gas and t is the CAD reaction time. Plots of CAD rate constants *vs* center-of-mass energy for all seven compounds are shown on Figure 3-8. The calculated values for E_o and k_o are summarized in Table 3-2.

$$k = k_o \frac{(E - E_o)^v}{E} \qquad (3\text{-}3)$$

$$\ln \frac{I}{I_o} = knt \qquad (3\text{-}4)$$

The calculated threshold fragmentation energy (*Eo*) values depend on the influence of the substituents R^1, R^2, and R^3. However, in all seven cases investigated, these values were found to be quite similar and indeed identical within experimental error (the experimental error was estimated in our previous studies [90JACS2471] to lie in the range 0.05 - 0.2 eV). While all experimentally calculated E_o values fall in a range of 0.05

- 0.3 eV, the slopes of the correlation curves differed significantly depending on the substituents. These slopes represent the dependence of the overall rate constant for the collisionally activated dissociation process on the average collision energy (center-of-mass) *E*. Thus, from the results of Figure 3-8, the dependence of the CAD pyrolysis rate constants as a function of *E* decrease as follows:

$$t\text{-Bu} > CH_3CHPh \sim CH_2CH_2Ph > i\text{-Pr} > \text{p-Et} \sim \text{Pr} \sim \text{m-Et}$$

A detailed theoretical treatment of collisionally activated dissociation reactions for ions as large as these has not been developed. However, the observed dependence of the rate constants on the center-of-mass energy may be ascribed either to collisions in converting kinetic to internal energy (groups with larger individual cross-section seem to have stronger dependence of *k* on *E*) or to differences in transfer of the collision energy into the reaction coordinate (vibration of the bond to be cleaved) of different reactive species. Detailed investigation of either of these explanations requires extensive theoretical development which is beyond the scope of the present study. As is to be expected, the order of the dependence of the CAD pyrolysis rate constants as a function of energy is the same as the observed order for the energy independent CAD scaling factor k_o, calculated from equation 3-3 (see Table 3-2).

The CAD studies were carried out using different reaction delay times to study a potential dependence of the reaction rates on the reaction time. The delay time was varied from very short times (0.05 sec) to extremely long reaction times (3 sec). No significant difference in the reaction rates was observed. The most likely explanation is that the fragmentation reaction occurs quite rapidly on the ICR time scale, so the longer delay times (> 100 ms) have no additional effect.

The rates of the vapor-phase pyrolysis reactions of esters have been extensively studied [75JCSPT(2)1025, 78JCSPT(2)1090, 71PPOC75, 83JCSPT(2)1875,

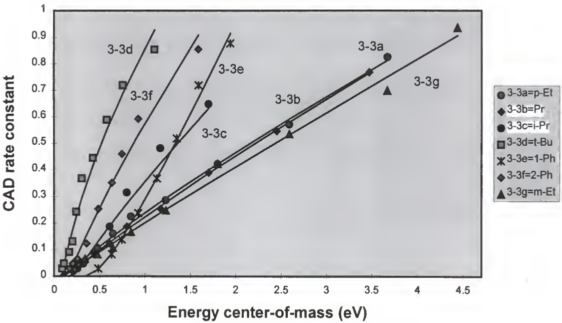


Figure 3-8. Kinetic Energy Center-of-Mass Plotted *vs*. CAD Rate Constant.

No	substituent	*Eo* (eV)	*ko*
3-3a	*p*-$CO_2CH_2CH_3$	0.07	146.0
3-3b	*p*-$CO_2(CH_2)_2CH_3$	0.10	143.8
3-3c	*p*-$CO_2CH(CH_3)_2$	0.16	262.3
3-3d	*p*-$CO_2C(CH_3)_3$	0.07	512.0
3-3e	*p*-$CO_2(CH_2)_2Ph$	0.34	363.1
3-3f	*p*-$CO_2CH(Ph)CH_3$	0.17	383.9
3-3g	*m*-$CO_2CH_2CH_3$	0.05	119.3

Table 3-2. Experimentally Calculated Values for the Threshold Fragmentational Energy E_0 and the Energy-Independent Scaling Factor k_o

84JCSPT(2)647, 87JCSPT(2)1683]. According to the generally accepted ester pyrolysis reaction mechanism, which involves a polarized transition state, α-substituents would have stronger influence on the rate than β-substituents. This was exactly the tendency found in this work. The *tert*-butyl substituted ester **3-3d**, which has three α-substituted methyl groups, decomposed the fastest. Secondary alkyl substituted esters were found to have intermediate rates of decomposition, while the primary alkyl substituted esters were the least reactive. The phenethyl substituted ester **3-3e** decomposed faster than the isopropyl ester **3-3c**; such an observation could be expected since a phenyl substituent has a larger influence on the reactive site than a methyl group. According to the literature reports [75JCSPT(2)1025, 78JCSPT(2)1090, 71PPOC75, 83JCSPT(2)1875, 84JCSPT(2)647, 87JCSPT(2)1683], the effect of the substituents on the rate correlation ratio is: tertiary >> secondary > primary. This is in agreement with our experimental results. However, the ratios tertiary/secondary and secondary/primary observed in our studies are much smaller than these found in the literature. This maybe related to the different (non-thermal) excitation process involved in ion activation in the FTICR experiments as compared to the (thermal) vapor-phase pyrolysis experiments.

For a comparison of the influence of the reactive position, compound **3-3g** with *meta*-ethoxycarbonyl substituent group was studied. The E_o value (0.05 eV) was found to be essentially the same as for the p-substituted analog. The pyrolysis reaction rates for both compounds were also very similar, as is to be expected for substituents with the same structure.

3.3. Summary and Conclusions

The cation tagging approach provides an efficient method of monitoring gas phase reactions which do not themselves involve charged species. The effect of various aliphatic and aromatic substituents on the fragmentation rate of the pyrolysis of ester reactions has been studied. Due to the stable positive charge present at the non-reactive site of the molecule at all times, the parent and fragment ions were detected, relative threshold fragmentation energies were calculated and a comparison between the rate of the pyrolysis reactions when different R groups are present were drawn. The fastest fragmentation was observed when the substituent is a tertiary alkyl group (*t*-butyl) and the slowest when the substituent is a primary alkyl group (ethyl or propyl).

CHAPTER 4

STUDY OF RADICAL MEROSTABILIZATION BY ELECTROSPRAY FTICR/MS

4.1. Introduction

It is well known that electron-withdrawing substituents stabilize carbon anions and electron-donating substituents stabilize carbon cations. Dewar first suggested [52JACS3353] that radicals should be particularly strongly stabilized when both an electron-withdrawing and an electron-donating substituent are present at the radical site. Katritzky [65MI1, 71MI1, 73H67, 74JCSPT(1)1422, 74JCSPT(1)1427] provided the first experimental evidence for such carbon-containing radicals and proposed the term "merostabilization" to describe this concept. Balaban [71RRC725, 74T73, 77T2249] independently developed the analogous concept of "push-pull" for nitrogen centered radicals. Later, Viehe [78ACIEE691, 79ACIEI917, 85ACR148] entered the field denoting these effects as "captodative". Merostabilization has been explained in terms of qualitative valence bond, molecular orbital and Linnett double quartet theories and supported by the prediction and synthesis of new stable radicals [73H67, 74JCSPT(1)1422, 74JCSPT(1)1427, 71RRC725, 77T2249, 79ACIEI917]. The concept provides a fundamental model for a better understanding of many properties of organic compounds, such as the chromophoric systems of indigo [80ACIEI908] and many heterocycles [89JHC885].

However, further research on the stabilization of radicals by the synergistic interaction of substituents has given rise to much controversy. Whereas many research results supported the synergistic donor/acceptor stabilization [79CJC2652, 80TL3681], others suggested that the merostabilization concept was not universally valid. Thus, Rüchardt and co-workers provided evidence suggesting that stabilization effects are additive and not synergistic [83CB3216, 87ACIEE573, 87ACIEE770, 95LA1483]. Korth *et al.* indicated the absence of kinetic stabilization for some radicals by measuring their absolute rates for dimerization by ESR spectroscopy [83JCSPT(2)67], Chambers *et al.* revealed that the synergistic effect was not dominant in systems containing polyfluoroalkyl groups [85JCSPT(1)2209], and certain theoretical calculations failed to reveal any additional stabilization [90JMS261].

Quantum mechanical calculations have been used to study merostabilization in radicals. Previous theoretical calculations from this group suggested that there was significant merostabilization energy in polar media, but not in the gas phase [86JACS7213, 90IJQC1, 91JOC134]. Pasto [88JACS8614] also found considerable extra stabilization in allyl-type three electrons radicals but not in other systems. Calculations had been carried out in water for carbon-centered radicals [94JMS41] and nitrogen-centered radicals [84JCSCC663], all of which confirmed merostabilization in various situations. ESR spectroscopy was widely employed in those studies [77T2249, 84JACS663, 87JCSPT(2)1077, 83JOC2989]. Bordwell and co-workers determined radical stabilization energies by equilibrium acidities [93ACR510]. Most of this research was qualitative or semi-quantitative. The present report gives a quantitative evaluation of the merostabilization concept by Fourier Transform Ion Cyclotron Resonance Mass Spectrometry (FTICR/MS) in the gas phase. In Chapter two of this thesis evidence that electrospray ionization coupled with FTICR/MS provides an excellent way to produce gaseous pyridinium ions from pyridinium salts in solution and to monitor the chemical behavior of the ions has been presented. In studies of collisionally activated dissociation of pyridinium cations [88AI155, 89OMS1017, 90JACS2471], the *N*-methylpyridinium cation was found to be very stable, undergoing essentially no dissociation. Therefore, a set of *N*-methylpyridinium salts as model compounds was selected to investigate radical merostabilization.

4.2. Results and Discussion

4.2.1. General Approach

The general strategy was to investigate the way in which the energy for the homolytic scission of the 4-(*β*-phenethyl)pyridinium cation would be affected by the presence of an electron donor or an electron acceptor substituent. If the merostabilization concept is correct, a suitably situated electron donor substituent should stabilize the pyridiniumylmethyl radical (Py^+-$CH^\bullet$-D) and hence facilitate the scission. The assumption here is that the C-C bond scission in all processes follows a similar potential energy curve, and that stabilization of the product determines the barrier; *i.e.* the intersection of the C-C bond breaking curve with the product formation curve. Thus, according to the Bell-Evans-Polanyi principle [36PRSL414, 38TFS11], the stabilization of the final state leads to the decrease of the transition barrier of the reaction.

4.2.2. Synthesis of the Model Compounds

Three *N*-methylpyridinium salts were prepared by Dr. Ming Qi with the help of Daniel Nichols (the synthetic routes are shown in Figure 4-1). 4-(Dibenzylmethyl)pyridine (**4-4**) and 4-(1,3-diphenyl-1-oxo-2-propyl)pyridine (**4-5**) were made starting from 4-picoline (**4-1**), by the sequential introduction either of two benzyl, or of one phenylacetyl and one benzyl group using modified literature methods [75S705].

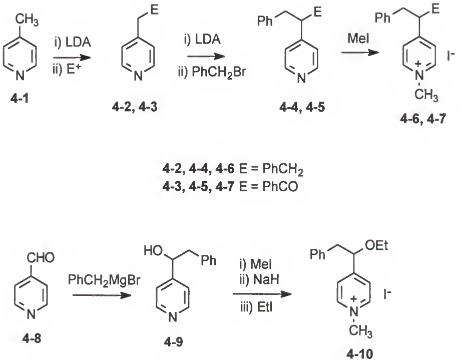


Figure 4-1. Synthesis of the Model Compounds **4-6**, **4-7** and **4-10**.

These two substituted pyridines **4-4** and **4-5** reacted with methyl iodide to form the corresponding *N*-methylpyridinium salts **4-6** and **4-7**. Compound **4-10** was prepared from 1-pyridyl-2-phenylethanol **(4-9)** following the procedure indicated in Figure 4-1.

4.2.3. Fragmentation Pathways

N-Methyl-4-(1,3-dibenzylmethyl)pyridinium iodide **(4-6)** (MW 415) was chosen as a model compound with a neutral substituent group. When CAD experiments were performed on the pyridinium cation **4-6**, the spectra showed three major ions (Figure 4-2): (i) the parent cation **4-11** at *m/z* 288, (ii) the radical cation of interest **4-12** at *m/z* 197 generated *via* loss of a benzyl radical from the parent ion, and (iii) cation **4-13** at *m/z* 196, obtained *via* loss of a hydrogen atom from the radical **4-12**. The ion at *m/z* 196 may possess the cyclic structure **4-13**, formed *via* ring closure as shown on Scheme 4-2 rather than compound **4-14** with a double bond. Fragmentation leading to the formation of stable cyclic structures was previously observed by us in an independent study of singly and multiply charged pyridinium cations [95JMS1581]. When the ion at *m/z* 197 was ejected, the ion at *m/z* 196 disappeared, proving that the ion at *m/z* 196 is formed from the radical at *m/z* 197 and not directly from the parent ion at *m/z* 288.

N-Methyl-4-(1,3-diphenyl-1-oxo-2-propyl)pyridinium iodide **(4-7)** (MW 429) was chosen as a model compound to study the effect of an electron withdrawing group (benzoyl) on the appearance potential. The CAD spectrum showed 5 major ions (Figure 4-3): (i) the parent cation **4-15** at *m/z* 302, (ii) the radical cation **4-16** at *m/z* 211, corresponding to loss of a benzyl radical from the parent cation, (iii) cation **4-17** at *m/z* 210, generated *via* loss of a hydrogen atom from the radical **4-16**, (iv) the radical cation **4-12** at *m/z* 197 corresponding to loss of a benzoyl radical from the parent ion, and (v) the cation **4-13** at *m/z* 196, generated *via* loss of a hydrogen atom from the radical cation **4-12**. As in the case of compound **4-6** (Figure 4-2) we believe that **4-13** is the right

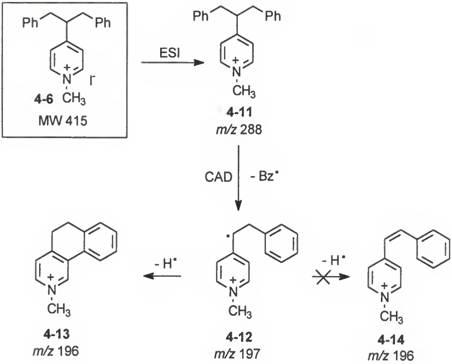


Figure 4-2. Fragmentation Pattern for Compound **4-6**.

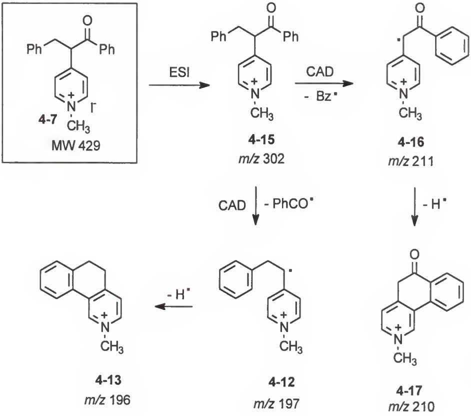


Figure 4-3. Fragmentation Pattern for Compound **4-7**.

structural representation. When the ions at *m/z* 211 and *m/z* 197 were respectively ejected from the cell *via* standard double resonance experiments, the corresponding ions at *m/z* 210 and *m/z* 196 disappeared, confirming the proposed fragmentation sequence. Since two different radical fragmentations were observed, it could be expected that these species (**4-12** and **4-16**) would have similar appearance potentials, which was later confirmed experimentally and supported by theoretical calculations.

N-Methyl-4-(1-ethoxy-2-phenylethyl)pyridinium iodide (**4-10**) (MW 369) was chosen as a model compound to study the effect of an electron donating group (ethoxy) on the appearance potential of the corresponding radical. For the CAD experiments the precursor cation **4-18** (*m/z* 242) was isolated using standard RF ejection pulses and was allowed to undergo collisions with argon atoms. In addition to the parent ion **4-18**, the CAD spectrum showed formation of three fragment ions (Figure 4-4): (i) *m/z* 151 generated *via* loss of a benzyl radical from the parent ion forming the radical cation of interest **4-19**; (ii) *m/z* 122 **4-20** corresponding to loss of ethyl radical from the radical cation **19**, and (iii) *m/z* 94 corresponding to methyl pyridinium ion **4-21**, generated *via* loss of a carbon monoxide molecule from the ion at *m/z* 122. To verify the fragmentation pathway we ejected the radical at *m/z* 151 and as a result, the ions **4-20** and **4-21** at *m/z* 122 and *m/z* 94 disappeared. It was thus confirmed that ions **4-20** and **4-21** are formed from fragmentation of the radical cation **4-19** and not directly from the parent ion.

4.2.4. Threshold Fragmentation Energies

Thresholds for the appearance of fragment ions allowed the estimation of threshold fragmentation energies (E_O) for the collisionally activated dissociation (CAD) in the gas phase of three substituted pyridinium cations to form the corresponding free radicals. The E_O values for the ions **4-11**, **4-15**, and **4-18** were calculated as described in Chapter 3. The translational energy (E_{ion}) imparted to an ion during the excitation stage

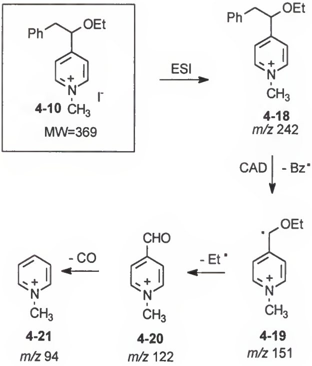


Figure 4-4. Fragmentation Pattern of Compound **4-10.**

of the FTICR CAD process is obtained from equation 4-1 [82AC96, 86IJMSIP93] where q is the ionic charge, V is the peak-to-peak amplitude of the RF excitation pulse, τ is the RF pulse width, m is the ionic mass, and d is the distance between the excitation plates of the analyzer cell.

$$E_{ion} = q^2 V^2 \tau^2 / 8md^2 \qquad (4\text{-}1)$$

$$E_{cm} = E_{ion} \times [M_{Ar} / (M_{Ar} + m)] \qquad (4\text{-}2)$$

The nominal center-of-mass energy (E_{cm}) can be calculated from equation 4-2, as described in Chapter 3, where M_{Ar} is the mass of the neutral gas (Ar) and m is the mass of the ion. In this present study we used again the modified version of the "CRUNCH" program, as described in Chapter 3 and shown in equation 4-3, where k is the observed CAD rate constant, k_O is an energy-independent scaling factor, E_O is the threshold energy and v is treated as a variable parameter.

$$k = k_O \times (E - E_O)^v / E \qquad (4\text{-}3)$$

$$ln\,(I / I_O) = knt \qquad (4\text{-}4)$$

The CAD rate constants are derived from the percent fragmentation observed (eq. 4), where (I / I_O) is the percent fragmentation observed, n is the number density of the collision gas and t is the CAD reaction time. Plots of CAD rate constants *vs* center-of-mass kinetic energy for all three cations **4-11**, **4-15**, and **4-18** are shown in Figure 4-5. In a previous study from this laboratory [90JACS2471], the absolute experimental errors in calculating E_o values were estimated to be up to 0.35 eV (8 kcal/mol) and relative experimental errors are expected to be lower for comparable systems. The experimental errors in the present report are expected to fall in the same range.

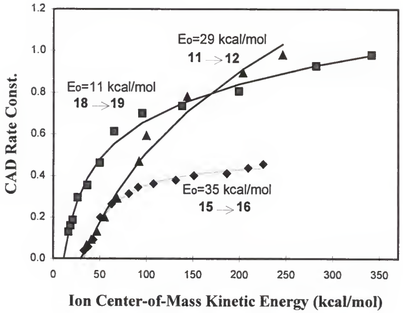


Figure 4-5. CAD Rate Constants Plotted *vs.* Ion Center-of-Mass Kinetic Energies (kcal/mol) to Yield the Threshold Fragmentation Energies *Eo* for Cations **4-11**, **4-15**, and **4-18**.

4.2.5. Radical Merostabilization

As seen in Figure 4-1, and determined from the computer fits (CRUNCH program) the observed threshold fragmentation energy (E_0) for pyridinium cations **4-11**, **4-15**, **4-18** are 29 kcal/mol, 35 kcal/mol and 11 kcal/mol, respectively. Assuming no significant difference in ground state stabilization of the starting materials, a lower E_0 means higher stability of the corresponding radical. Therefore, radical **4-19** demonstrated significant stabilization ($\Delta Eo \approx 20$ kcal/mol) compared to radical **4-12**, (which has only one electron-accepting group: pyridinium ion Py+) and radical **4-16**, (which has two electron-accepting groups: pyridinium ion and benzoyl). This strongly supports the concept of radical merostabilization, that an electron-accepting group (pyridinium ion) and an electron-donating group (ethoxy) can significantly stabilize a radical. The pyridinium ion is a very effective electron-accepting group and only a very small difference of stabilization was found between radicals **4-12** and **4-16**, and as expected pyridinium cation **4-15** gives two radicals, **4-12** and **4-16,** in the CAD experiments.

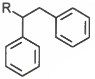
4.2.6. Theoretical Calculations

To support the experimental results, AM1 [85JACS3902] and PM3 [89JCC209] quantum-chemical calculations were performed by Dr. Toomas Tamm, using the Unrestricted Hartree-Fock (UHF) Hamiltonian as implemented in the AMPAC 5.0 program package [94MI1]. Neither of these semiempirical methods has been parametrized specifically for calculation of the properties of transition states involving radical species or UHF wave functions. It was therefore considered necessary to perform these calculations with both parameterizations (AM1 and PM3) in parallel to decrease the chances of model errors biasing the results. As shown later, the results obtained are similar for the two parameterizations used. In general the AM1 model produces heats of formation within ± 7 kcal/mol and the PM3 model ± 4 kcal/mol for compounds of this type [91MI2]. Neutral closed-shell systems are more accurately reproduced than are radicals and cations [91MI1]. Since the energy differences for rather similar processes are compared, such errors are expected to be systematic. Considerably less is known about barriers to reactions, and the UHF method, in general, might be expected to over-estimate them. Comparison of the observed fragmentation energies with our calculated barriers suggest that this might be the case in the present study: the energy required to break a C-C single bond could be somewhat too high. The relative barriers, however, depend on the intersection of this potential energy surface with that of the relative heats of formation of the products. Throughout all the calculations, all stationary points were additionally characterized by calculations of the Hessian (force-constant) matrix. All minima were confirmed with no negative eigenvalues and all transition state geometries had a single negative eigenvalue of the Hessian.

Due to the nature of the semiempirical parametrization, the zero-point vibrational energies are included in the parameters and need not be added explicitly. This assumption was verified for several calculated geometries and energy differences. It was indeed found that the inclusion of the zero-point energies did not affect the results significantly.

Dissociation paths were initially characterized by stepwise increasing the length of the breaking bond, while optimizing all other coordinates at each given bond length. The resulting potential energy curves are presented in Figure 4-6. From the points with the highest energy, the transition state geometries were refined using the eigenvector following procedure [86JCC385]. It can be concluded that the height of the reaction barrier ($\Delta H^{\ddagger}$), as well as the overall thermodynamic stabilization are about 10 kcal/mol lower for cation **4-18** (see Table 4-1), containing an electron-donor and an electron-acceptor group as compared to cations with one neutral and one electron-accepting group (**4-11**) or two electron-accepting groups (**4-15**) attached in the dissociation product to the carbon radical center.

In another series of calculations, full geometry optimizations were performed, again by Dr. Toomas Tamm, for the reactants and products of the dissociation reactions, as well as for a series of similar comparison reactions, where the electron-accepting methylpyridinium group was replaced by a neutral phenyl group; in these compounds (**4-22**, **4-23** and **4-24**) (see Scheme 4-7) with the effect of an electron-acceptor substituent eliminated, no radical stabilization should be found. Heats of radical formation (ΔH_R) were calculated for all cases as summarized in Table 4-1. The dissociation energy of cation **4-18** is significantly lower than that of the cations **4-11** or **4-15**, in agreement with the experimental results. However, where the electron-accepting group (pyridinium) is replaced by a neutral group (phenyl) no evidence for stabilization is found, not only in the heats of the dissociation reaction of compounds **4-22** and **4-23** but also that for **4-24**. For compounds **4-15** and **4-18**, the AM1 calculated transition state energies ($\Delta H^{\ddagger}$) are slightly lower than the corresponding heats of radical formation (ΔH_R), due to the different methods of calculation of these quantities. The ΔH_R calculations involved heats of formation of isolated products (corresponding to infinite separation), whereas in the $\Delta H^{\ddagger}$ calculations, the products were separated by a small finite distance and the energy of the system is lowered by the charge-dipole interactions between the products.



4-22 R = CH_2Ph

4-23 R = COPh

4-24 R = OEt

Figure 4-7. Structures for Compounds **4-22, 4-23** and **4-24.**

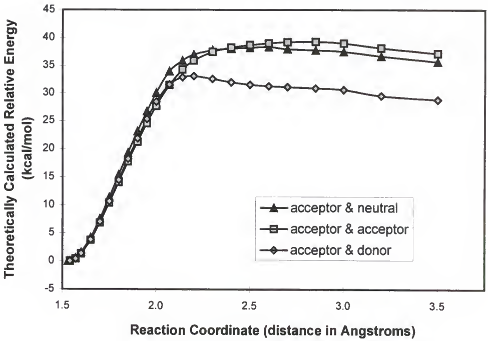


Figure 4-6. Theoretically Calculated Relative Energy (kcal/mol) Plotted *vs.* Reaction Coordinate. The Reaction Coordinate Listed is the Distance of the C-C Bond Being Broken, Minimizing the Energy with Respect to All Other Molecular Coordinates.

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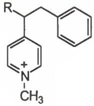
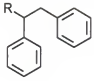
<td colspan="7">
4-11 R=CH2Ph
4-15 R=COPh
4-18 R=OEt</td>
<td colspan="3">
4-22 R = CH_2Ph
4-23 R = COPh
4-24 R = OEt</td>
</tr>
<tr><td>cpds</td><td colspan="2">**4-11**</td><td colspan="2">**4-15**</td><td colspan="2">**4-18**</td><td>**4-22**</td><td>**4-23**</td><td>**4-24**</td></tr>
<tr><td>gps[a]</td><td colspan="2">A & N</td><td colspan="2">A & A</td><td colspan="2">A & D</td><td>N & N</td><td>N & A</td><td>N & D</td></tr>
<tr><td></td><td>$\Delta H^{\ddagger}$</td><td>ΔH_R</td><td>$\Delta H^{\ddagger}$</td><td>ΔH_R</td><td>$\Delta H^{\ddagger}$</td><td>ΔH_R</td><td>ΔH_R</td><td>ΔH_R</td><td>ΔH_R</td></tr>
<tr><td>AM1</td><td>38</td><td>38</td><td>39</td><td>40</td><td>31</td><td>32</td><td>33</td><td>35</td><td>33</td></tr>
<tr><td>PM3</td><td>37</td><td>36</td><td>41</td><td>41</td><td>32</td><td>29</td><td>33</td><td>36</td><td>32</td></tr>
</table>

[a] D = electron donor; A = electron acceptor; N = neutral

Table 4-1. Theoretically Calculated Heats of Reaction (ΔH_R) and Energies of Transition States ($\Delta H^{\ddagger}$) (all in kcal/mol).

The merostabilization energy (E_M) of a radical with an electron-donor (D) and an electron-acceptor (A) groups attached simultaneously to the carbon radical center (*e.g.* radical **4-19**) is defined as shown in eq. 4-5, where E_{DA} is the energy of the radical studied (**4-19**), E_{DD} is the energy of a radical with two electron-donor groups (such as radical **4-32**, Figure 4-8) and E_{AA} is the energy of the radical with two electron-acceptor groups at the radical center (such as radical **4-29**, Figure 4-8).

The calculated merostabilization energy (E_M) of radical **4-19** is artificially lowered because the heat of formation of the AA species (E_{AA}) is additionally enhanced due to the intramolecular charge-charge repulsion between two positively charged methyl pyridinium groups. In order to eliminate this contribution to the merostabilization energy, we have used the difference between the calculated E_M values of the parent ion **4-18** ($E_{M\ ion}$, calculated using structures **4-18**, **4-28**, and **4-25**, respectively) and of the radical **4-19** ($E_{M\ rad}$) as the characteristics of the merostabilization (equation 4-6).

$$E_M = E_{DA} - 1/2\,(E_{DD} + E_{AA}) \qquad (4\text{-}5)$$

$$\Delta E_M = (E_{M\ rad}) - (E_{M\ ion}) \qquad (4\text{-}6)$$

When both an electron-donor (OEt) and an electron-acceptor (methylpyridinium) groups are present, as for radical **4-19**, a significant additional stabilization of the radical was observed ($\Delta E_M \sim$ 8-10 kcal/mol) (see Table 4-2). For a comparison, the calculated analogous energy difference (ΔE_M) was much smaller for radicals **4-12** and **4-16**, containing the electron-accepting methylpyridinium group and the mesomerically inactive benzyl group, and two electron-acceptor groups (benzoyl and methylpyridinium), respectively (see Table 4-2)*. Therefore, these calculations indicate the presence of a certain merostabilization of the radical with an electron-accepting and an electron-donating group simultaneously bonded to a carbon radical center.

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* For ion **11**, E_{DD} is calculated from **26** and E_{AA} from **25**

4.3. Summary and Conclusions

The existence of merostabilization in the system investigated is supported by both our experimental and theoretical calculations. It was clearly shown that when both an electron-donor and an electron-acceptor group are present at the radical site, significant additional stabilization was achieved. For comparison, when in the same system the electron-donor group was replaced by an electron-acceptor or a neutral group, no additional stabilization was observed.

For ion **15**, E_{DD} is calculated from **27** and E_{AA} from **25**
For ion **18**, E_{DD} is calculated from **28** and E_{AA} from **25**
For radical **12**, E_{DD} is calculated from **30** and E_{AA} from **29**
For radical **16**, E_{DD} is calculated from **31** and E_{AA} from **29**
For radical **19**, E_{DD} is calculated from **32** and E_{AA} from **29**

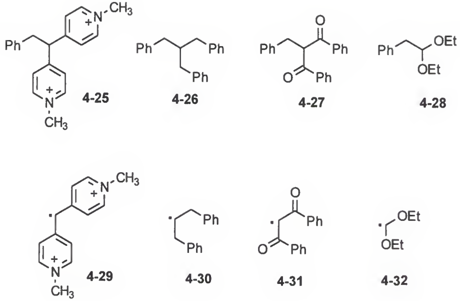


Figure 4-8. Structures **4-25** - **4-32** for Calculation of the Merostabilization Energies.

I: Neutral & Acceptor Substituents

	Heat of Formation			$E_M$ion	Heat of Formation			$E_M$rad	ΔE_M
cpds	**4-11**	**4-25**	**4-26**	**4-11**	**4-12**	**4-29**	**4-30**	**4-12**	
AM1	217	441	53	-30	216	441	56	-32	-2
PM3	217	436	54	-28	213	432	59	-32	-4

II: Acceptor & Acceptor Substituents

	Heat of Formation			$E_M$ion	Heat of Formation			$E_M$rad	ΔE_M
cpds	**4-15**	**4-25**	**4-27**	**4-15**	**4-16**	**4-29**	**4-31**	**4-16**	
AM1	197	441	9	-28	198	441	15	-30	-2
PM3	191	436	4	-29	192	432	9	-29	0

III: Donor & Acceptor Substituents

	Heat of Formation			$E_M$ion	Heat of Formation			$E_M$rad	ΔE_M
cpds	**4-18**	**4-25**	**4-28**	**4-18**	**4-19**	**4-29**	**4-32**	**4-19**	
AM1	152	441	-90	-24	145	441	-83	-34	-10
PM3	154	436	-76	-25	144	432	-78	-33	-8

Table 4-2. Calculation of Merostabilization Energies. All values are given in kcal/mol.

CHAPTER 5

GAS PHASE INVESTIGATIONS OF SULFONIUM SALTS BY ELECTROSPRAY FTICR/MS

5.1. Introduction

Sulfur-containing compounds play an important role in biological systems and synthetic organic chemistry. A comprehensive review of mass spectrometric studies of neutral S-containing compounds, such as sulfides, disulfides, sulfoxides, and sulfones has recently been published [95MSR117]. However, only limited reports of the mass spectrometric investigations of gas phase fragmentations of sulfonium salts have appeared, and most of these discuss onium ions in general, concentrating on ammonium and phosphonium salts. It is clear from this published work that sulfonium salts easily undergo fragmentation in the gas phase by heterolysis, to generate the corresponding neutral sulfides. In general, sulfonium salts are more stable than oxonium salts, but less stable than phosphonium and ammonium salts.

In an important recent paper, relative rates of gas-phase dissociation for the reaction $RS(CH_3)_2^+ \longrightarrow R^+ + S(CH_3)_2$, where R = p-CH_3OPhCH_2, p-CH_3PhCH_2, Bz, p-$ClPhCH_2$, and p-NO_2PhCH_2, were determined using tandem positive-ion liquid secondary ion mass spectrometry [96JOC2753]. Heterolytic cleavages of the S-R bonds were observed for all five sulfonium salts studied. The Hammett plot for the dissociation of these ions was linear, which suggests that the dissociation mechanism was the same across the series; however, the authors concluded that there were insufficient experimental data to assign the dissociation mechanism. On the basis of semiempirical calculations, a direct dissociation pathway was suggested, since no distinct transition states and no stable structures, corresponding to ion-molecule complexes on the potential energy surface, were found.

Mass spectrometric studies utilizing field desorption (FD) ionization [75AC1165], desorption/ionization [94JPOC465], ^{252}Cf plasma desorption (^{252}Cf-PD) [88OMS705], and fast atom bombardment (FAB) [88OMS705] all concluded that vaporization of sulfonium salts formed clusters of the type $[2CAT^{+}.AN^{-}]^{+}$. In each case the base peak corresponded to the molecular ion, and the fragmentation generated species of type $RS^{+}=CHR'$.

The gas phase guest-host complexation chemistry of methoxycalix[6]arene and methoxycalix[8]arene with $Et_3S^{+}BF_4^{-}$ has been investigated [94JPOC465]. FAB and continuous flow liquid secondary ionization (CF-LSI) mass spectrometry have been used for monitoring peptido leukotriene systems with attached ternary sulfonium groups [94JASMS292]. The tertiary sulfonium compound DMSP (3-dimethylsulfoniopropionate), found in marine algae and plants, has been analyzed by ^{252}Cf-PD TOF/MS [95JMS1187], FAB/MS [94AJPP37, 94PP103], and GC/MS (after derivatization) [94JAPP37] techniques.

Ion/molecule reactions of the methylenedimethylsulfonium radical cation have been studied in detail by Fourier transform ion cyclotron resonance mass spectrometry (FTICR/MS) [93OMS1623]. Reactions of this radical cation with dimethyl sulfide to form a product corresponding to the abstraction of a thiomethyl radical were discussed.

Sulfonium ions resulting from the hydrolysis and subsequent condensation of some chemical warfare agents have been studied by secondary ionization (SI) [95EST2107], thermospray liquid chromatography (TLC) mass spectrometry [89MI1], [95JMS1716], and GC (gas chromatography) [87MI2, 88MI1] mass spectrometry. Rohrbaugh and Yang [88MI1, 89MI1, 89PSS17] and Munavalli *et al.* [87MI2, 95JMS1716] have studied sulfonium ions as intermediate products of the decomposition reactions of chemical warfare agents such as *bis*(2-chloroethyl)sulfide (HD or mustard). When thermospray mass spectrometry was used for investigation of chemical agents, stable three-membered cyclic sulfonium ion intermediates were detected [89MI1, 95JMS1716]. Using GC/MS, sulfonium chlorides and their decomposition products, which include mustard gas, were studied and decomposition reaction pathways were proposed [87MI2, 89PSS17]. Aqueous solutions containing sulfonium chlorides have also been studied by GC/MS and thermal decomposition to the corresponding sulfides was observed [87MI2]. The formation of dimeric sulfonium salts as a result of the decomposition of dithioesters of the type $RSCH_2CH_2Cl$, where R = methyl, ethyl, phenyl and benzyl, was also reported within the same study [88MI1].

Neutralization-reionization mass spectrometry investigations of sulfides that lead to the generation of sulfur radicals and sulfonium ions also appear in the literature [92JACS7146, 94JPC4845].

This study discusses the gas phase behavior and ion-molecule reactions of sulfonium salts using electrospray ionization (ESI) coupled with FTICR/MS. The advantages of using ESI FTICRMS for studying singly [96JACS1] and doubly [95JMS1581] charged organic species have already been shown in Chapter 2 of this thesis. To the best of our knowledge there are no previous reports of the use of ESI/MS for studying sulfonium salts.

5.2. Results and Discussion

A variety of sulfonium salts were studied by electrospray FTICR/MS. All samples were dissolved in 49/49/2 (volume ratio) water/methanol/acetic acid solution at a concentration of 0.1 mg/mL and were sprayed at a flow rate of 1 µl/min.

5.2.1 Fragmentation Pathways.

When compound **5-1** was sprayed in the gas phase, it underwent immediate fragmentation to more stable species (Figure 5-1). The parent ion **5-2** was not detected, even when no RF energy was applied to the system. The two fragments observed were: (i) the base peak corresponding to cation **5-3** at *m/z* 167, generated *via* loss of a dimethyl sulfide molecule from **5-2**, and (ii) a minor peak corresponding to cation **5-4** at *m/z* 165 generated from **5-3** *via* loss of a hydrogen molecule.

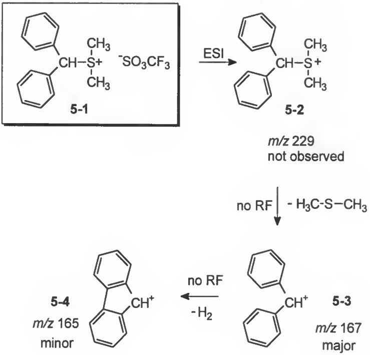


Figure 5-1. Fragmentation Pattern for Compound **5-1**.

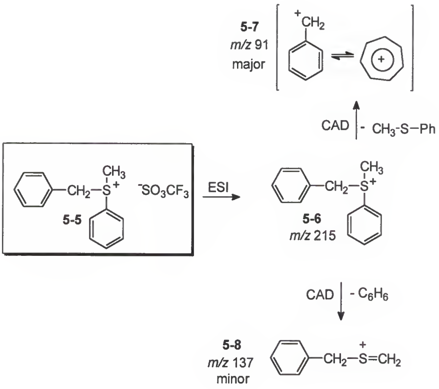
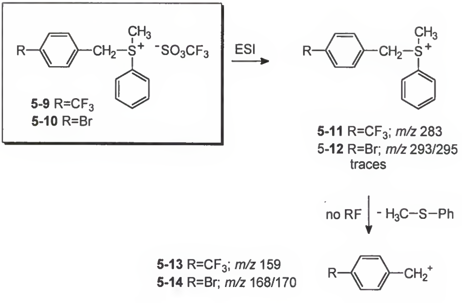


Figure 5-2. Fragmentation Pattern for Compound **5-5**.

Compound **5-5** was more stable: the parent ion **5-6** at *m/z* 215 was the only peak detected initially (Figure 5-2). When **5-6** was subjected to collisionally activated dissociation (CAD) reactions with neutral argon, two fragment ions were observed: (i) the tropylium/benzyl ion **5-7** at *m/z* 91 as the major peak and (ii) **5-8** at *m/z* 137 generated *via* loss of a benzene molecule from the parent ion as the minor peak.

The mass spectra of compounds **5-9** and **5-10** illustrate the effect of substituents on the fragmentation pattern. In both cases, only traces of the parent ions **5-11** at *m/z* 283 and **5-12** at *m/z* 293/295 (corresponding to ^{79}Br and ^{81}Br, respectively) were detected (Figure 5-3). The base peaks, corresponding to the fragment ions **5-13** at *m/z* 159 and **5-14** at *m/z* 168/170, respectively, were generated *via* loss of a methyl phenyl sulfide molecule from the parent ions **5-11** and **5-12**.

Compounds **5-15**, **5-16**, and **5-26**, variously substituted at the aroyl group, further explore the effect of structural variation (Figure 5-4). When compounds **5-15** and **5-16** were sprayed in the gas phase, the only ions detected corresponded to the parent ions **5-17** at *m/z* 273 and **5-18** at *m/z* 321/323, respectively. CAD reactions of **5-17** and **5-18**, using neutral argon, led to loss of a methyl phenyl sulfide molecule generating major fragment ions **5-19** at *m/z* 149 and **5-20** at *m/z* 197/199, respectively; minimal RF energy was required, due to the effect of the electron-donating substituents. Ions **5-19** and **5-20** eliminated carbon monoxide to form cations **5-21** at *m/z* 121 and **5-22** *m/z* 169/171, respectively. Another fragment ion **5-23** at *m/z* 124 was formed from both **5-17** and **5-18** *via* homolytic cleavage of the carbon-sulfur bond. Cations **5-24** at *m/z* 135 and **5-25** at *m/z* 183/185, were generated in small amounts from **5-17** and **5-18**, respectively, when high RF energy was applied (Figure 5-4). Compound **5-26,** with an electron-withdrawing



5-9 R=CF_3
5-10 R=Br

5-11 R=CF_3; *m/z* 283
5-12 R=Br; *m/z* 293/295
traces

5-13 R=CF_3; *m/z* 159
5-14 R=Br; *m/z* 168/170

Figure 5-3. Fragmentation Patterns for Compounds **5-9** and **5-10**.

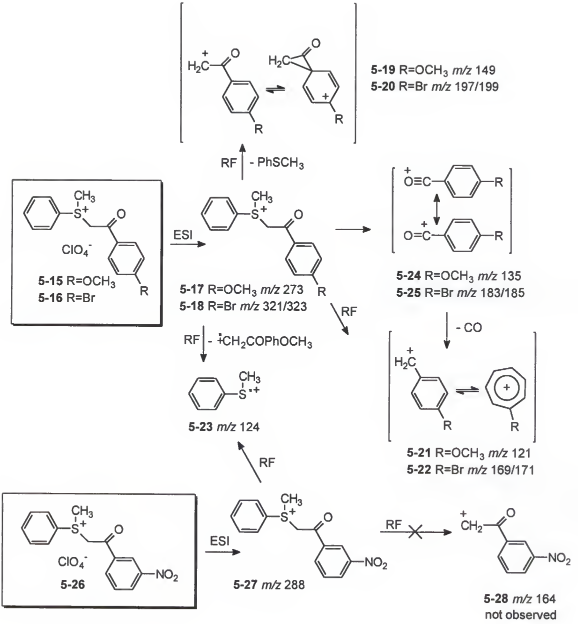


Figure 5-4. Fragmentation Patterns for Compounds **5-15**, **5-16** and **5-26**.

substituent at the *m*-position of the aroyl group, displayed, as expected, a fragmentation spectrum very different to compounds **5-15** and **5-16** (Figure 5-4). Parent ion **5-27** at *m/z* 288 generated the only fragment ion **5-23** at *m/z* 124 *via* homolytic scission of the carbon-sulfur bond. No loss of methyl phenyl sulfide to afford **5-28** at *m/z* 164 was observed, which can be explained by the destabilization effect of the electron-withdrawing nitro group.

The convenience and suitability of electrospray mass spectrometry for studying doubly charged pyridinium salts [95JMS1581] has already been discussed in Chapter 2 of this thesis. However, when the doubly charged sulfonium salt **5-29** was sprayed, the expected doubly charged cation **5-30** at *m/z* 108.5 was not observed; apparently it undergoes immediate fragmentation *via* loss of a methyl cation to give the more stable singly charged cation **5-31** at *m/z* 202 (Figure 5-5). Ion **5-31** can further fragment *via* loss of a pyridinium group to generate **5-32** at *m/z* 123. In our previous study [95JMS1581] we observed that doubly charged cations are detected in higher relative intensities when the concentration of the doubly charged ion in the spraying solution is lower. However, in this case, **5-30** was not observed even when the initial solution was diluted twofold and threefold.

Four sulfonium salts **(5-33 - 5-35, 5-41)**, each with two phenyl groups and a different alkyl substituent at the sulfur atom, were investigated. Compound **5-33** generated parent ion **5-36** at *m/z* 215, which when subjected to CAD studies, using neutral argon, gave only **5-39** at *m/z* 187 generated *via* proton transfer and loss of ethylene (Figure 5-6). However, for compound **5-34**, loss of CH_2 from the parent ion **5-37** at *m/z* 201 is highly unlikely, and the CAD spectrum of **5-34** displayed only the

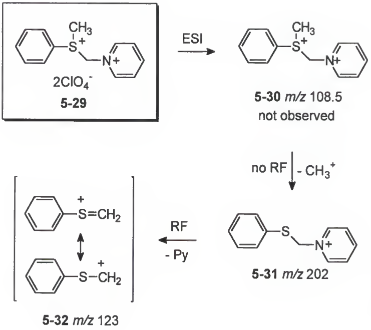


Figure 5-5. Fragmentation Pattern for Compound **5-29**.

diphenylsulfonium radical cation **5-40** at *m/z* 186. Compound **5-35** behaved just as **5-33**: the parent ion **5-38** at *m/z* 263/265, (corresponding to $^{35}Cl/^{37}Cl$) gave only the proton transfer product **5-39** at *m/z* 187. Figures 5-7 and 5-8 display the CAD spectra of compounds **5-33** and **5-34**, showing fragment ions **5-39** and **5-40**, respectively.

Compound **5-41,** with a cyclopropyl substituent, had possible fragmentation patterns *via* proton transfer and loss of a propylene molecule or *via* direct loss of the cyclopropyl group. The parent ion **5-42** at *m/z* 227 on CAD study, fragmented forming ions: i) **5-39** at *m/z* 187 generated *via* proton transfer and loss of C_3H_4, ii) the diphenylsulfonium radical cation **5-40** at *m/z* 186 and iii) **5-43** at *m/z* 149 generated *via* loss of a phenyl group from the parent ion (Figure 5-9).

5.2.2. Attempted Ion/Molecule Reactions.

Ion-Molecule Reactions. Nucleophilic substitution reactions proceed via replacement of a leaving group (X) attached to an aliphatic carbon atom (R) by a nucleophile (Nu): $Nu + RX \rightarrow NuR + X$. These reactions can be unimolecular, where the rate of the reaction depends only on the substrate and it is independent of the nucleophile or bimolecular, where the rate is first order both in the nucleophile and in the substrate concentration. Unimolecular reactions follow an S_N1-type mechanism which involves two distinct steps:(i) formation of carbocation R^+ and X' and (ii) reaction of R^+ with the nucleophile [69MI418]. Bimolecular reactions follow a direct S_N2-type displacement which occurs *via* a transition state as shown on Figure 5-10.

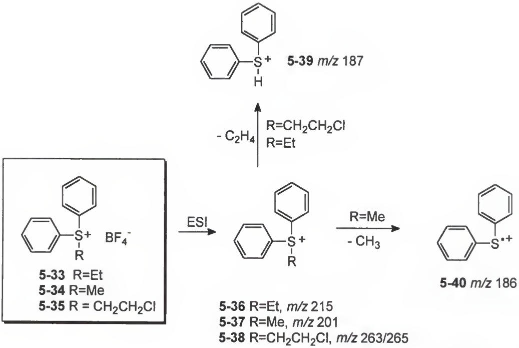


Figure 5-6. Fragmentation Patterns for Compounds **5-33**, **5-34** and **5-35**.

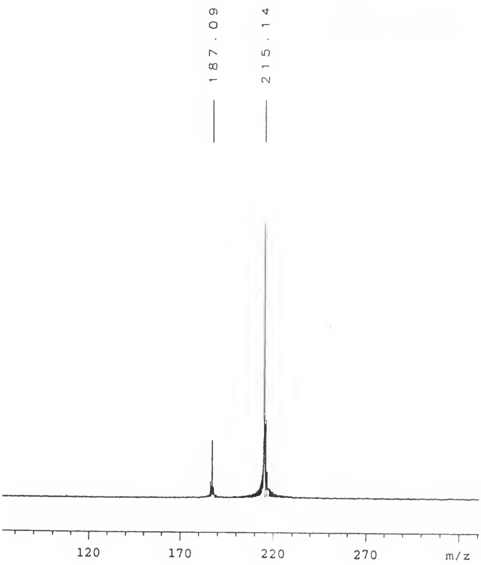


Figure 5-7. Fragmentation Pattern of Compound 5-33.

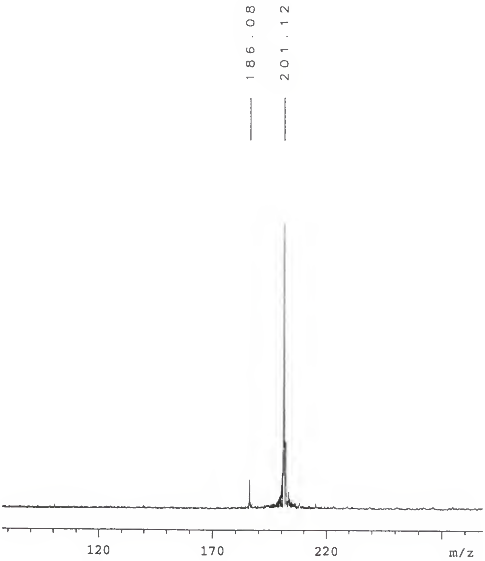


Figure 5-8. Fragmentation Pattern of Compound **5-34**.

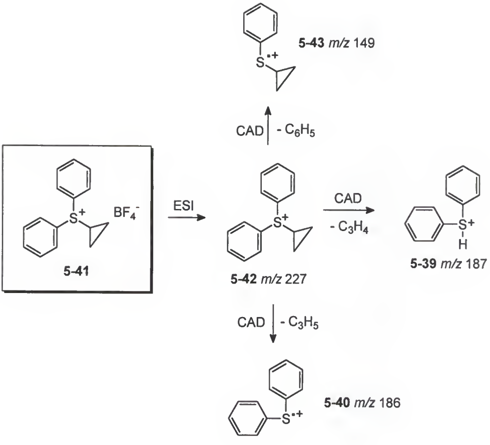


Figure 5-9. Fragmentation Pattern for Compound **5-41**.

$$\boxed{\mathrm{Nu + RX \longrightarrow NuR + X}}$$

$$\mathbf{S_N1}\text{:}\quad \text{(i) } \mathrm{R{-}X} \xrightarrow{\text{slow}} \mathrm{R^+ + X^-}$$

$$\text{(ii) } \mathrm{Nu + R^+} \xrightarrow{\text{fast}} \mathrm{{}^+Nu{-}R}$$

$$\mathbf{S_N2}\text{:}\quad \text{(i) } \mathrm{Nu + R{-}X} \xrightarrow{\text{slow}} \left[\mathrm{Nu{\cdots}R{\cdots}X}\right] \xrightarrow{\text{fast}} \mathrm{{}^+Nu{-}R + X^-}$$

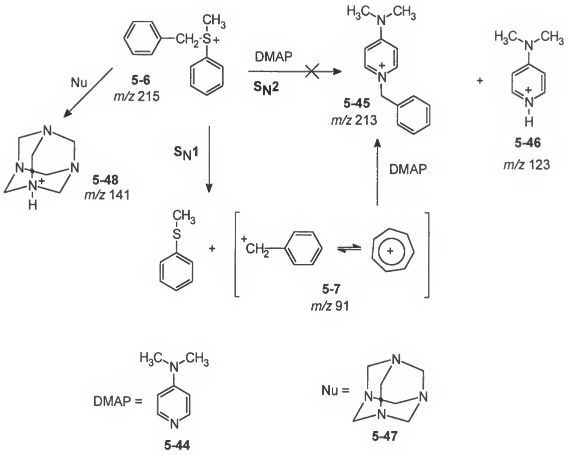
Figure 5-10. S_N1 and S_N2 Reaction Mechanisms.

Existence and detection of S_N2 reactions of gas phase is still a controversial topic. On the basis of both experimental and theoretical work, Brauman and co-workers demonstrated [77JACS4219, 86JCP471, 86JCP3559, 95JMS1649] that gas phase S_N2 reactions proceed over a potential energy surface with double-minima separated by a barrier, and that the energy of the reactants is higher than that of this transition state. The two minima correspond to ion-dipole complexes that form as stable intermediates on either side of the transition state. The formation and isolation of stable intermediates in the gas-phase substitution reactions, and the activation of those intermediates to form products [91JACS9696], strongly support Brauman's conclusions.

Literature reports of S_N2 reactions between a neutral nucleophile and a cationic substrate are quite limited [95JCS(CC)547, 95JOC1990, 96JOC2374]. We have previously studied the propensity towards S_N1 and S_N2 reaction mechanisms for a variety of systems (Chapter 2). We have shown evidence for intramolecular S_N2-type reactions in the gas phase [96JACS3]. However, so far we have not detected intermolecular S_N2 reactions [90JACS2471, 95JMS1581].

Results and Discussion. The solvolysis reactions of **5-1** have been recently studied and the product relationships in EtOH-H_2O were consistent with S_N1 type reactions [96JOC7256]. Compound **5-5**, which displayed a strong stable peak corresponding to the parent ion, was also chosen for investigating gas phase ion/molecule reactions. Based on our previous investigations of ion/molecule reactions in the gas phase, dimethylaminopyridine (DMAP) [95JMS1581] and hexamethylenetetramine [96JACS2] were chosen as nucleophiles and introduced into the cell *via* a leak valve. The pressure (*ca.* 5 x 10^{-7} Torr) was varied until the best conditions were found.

Compound **5-5** reacted with DMAP to give four peaks: (i) parent ion **5-6** at *m/z* 215, (ii) tropylium/benzyl ion **5-7** at *m/z* 91 formed from **5-6**, (iii) the expected product **5-45** at *m/z* 213, and (iv) protonated DMAP **5-46** at *m/z* 123. The two possible pathways for the formation of **5-45** are: (i) *via* S_N1 reaction **5-6** → **5-7** followed by **5-7** + **5-44** to give **5-45**, or (ii) *via* S_N2 mechanism of **5-6** + **5-44** (possibly *via* an ion/molecule pair) (see Scheme 5-8). To distinguish between these possibilities, **5-7** was completely ejected from the cell and as a result **5-45** disappeared, proving that **5-45** was formed *via* an S_N1



Scheme 5-11. Ion-Molecule Reactions of Compound **5-6**.

mechanism. We have previously observed and reported similar results for ion/molecule reactions of ammonium cations [95JMS1581].

Ion/molecule reactions attempted using hexamethylenetetramine **5-47** as a nucleophile, showed as the only ions detected: (i) parent ion **5-6** at *m/z* 215, (ii) protonated nucleophile **5-48** at *m/z* 141, and (iii) tropylium/benzyl ion **5-7** at *m/z* 91 formed *via* fragmentation of **5-6** (see Scheme 5-11).

5.3 Experimental

Compounds **5-1, 5-5, 5-9** and **5-10** were synthesized in one of our groups and are reported elsewhere [96JOC7256, 89MI2]. Compounds **5-15, 5-16, 5-26** and **5-29** were synthesized in another of our group's laboratory and are described elsewhere [75JCSPT(1)2489]. Compounds **5-33** and **5-34** were purchased from Lancaster and compounds **5-35** and **5-41** were purchased from Aldrich: the structures of all compounds were checked by NMR.

5.4 Conclusions

ESI FTICR/MS has previously been applied for studying successfully singly and doubly charged pyridinium cations, their fragmentation pathways and ion/molecule reactions (Chapter 2) and these applications have now been extended to sulfonium salts. Fragmentation patters of sulfonium cations were studied and the formation of sulfonium radical cations *vs*. protonated sulfonium cations depending on the parent ion structure was explained. The effect of electron-withdrawing and electron-donating groups on the dissociation processes was also investigated and it was shown that electron donating groups, as expected, have strong stabilizing effects while electron-withdrawing groups have strong destabilizing effects. The results of the ion/molecule reactions studied confirmed our previous findings [94OMS96, 95JMS1581] that S_N1 reaction mechanisms predominate in the gas phase. To date intermolecular S_N1-type reactions for pyridinium and sulfonium cations have been detected exclusively, however, we have recently shown evidence for the existence of intramolecular S_N2-type reaction in gas phase [96JACS3].

CHAPTER 6

SUMMARY AND CONCLUSIONS

Electrospray ionization (ESI), with its "soft" ionizing power when combined with the exceptional features of Fourier transform ion cyclotron resonance mass spectrometry (FTICR/MS), such as ultrahigh mass resolution, long ion storage time, capability of tandem mass spectrometry, high sensitivity and wide molecular range detection, provides an extremely powerful and versatile tool for gas phase investigations.

From the broad spectrum of possible applications of FTICR/MS, this thesis describes the investigation of gas phase properties of organic salts that exist in solution as charged species. Using the advantages provided by gas phase investigations as compared to solution phase, such as species simplicity and lack of solvent interferences, we have explored in detail the fragmentation pathways and ion-molecule reactions of a variety of singly and multiply charged pyridinium and sulfonium salts.

Organic salts containing two positive charges are relatively unstable and difficult to detect using mass spectrometric techniques and therefore the available literature discussing the gas phase properties of such species is still limited. The production and detection of doubly charged organic cations were studied using a previously unreported approach - electrospray ionization FTICR/MS. Three different doubly charged pyridinium salts were chosen as model compounds and subjected to collisionally activated dissociation (CAD) studies for identification of fragmentation pathways. The corresponding doubly charged cations were detected and, where possible, further subjected to CAD for identification of ion/molecule reaction mechanisms such as S_N1 and S_N2 type reactions. In all cases S_N1 reaction mechanisms were observed, in agreement with previously published work [90JACS2471].

Mass spectrometric investigations are limited by the detection of only charged species. However, there are numerous chemical reactions that occur without formation of charged species as intermediates or products and therefore their monitoring in the gas phase by mass spectrometric techniques is not very easy. The "cation tagging" approach was proposed, where a stable positive charge (tetraphenylpyridinium) is introduced at one end of the system, so the reaction that occurs at the other end can be easily monitored using mass spectrometric techniques. Seven different tetraphenylpyridinium esters were chosen as model compounds for studying gas phase pyrolysis reactions by FTICR/MS CAD using the cation tagging technique. The presence of the cation "tag" enabled us to calculate threshold fragmentation energies and predict the dissociation rate constants for all starting materials and compare their observed fragmentation rates.

The theory of radical stabilization, first proposed by Dewar and further developed by Katritzky as merostabilization and, later, by Viehe as capto-dative effect, is still controversial. There are numerous reports in the literature discussing this theory, some confirming it, some questioning its generality. Electrospray ionization FTICR/MS was used for calculating threshold fragmentation energies (E_O) as a measurement of stability. Three different 4-(1′-substituted-2′-phenethyl)-1-methylpyridinium salts containing a neutral, an electron-donor or an electron-acceptor group as α-substituent, respectively, were chosen as model compounds. *N*-Methyl-4-(1-ethoxy-2-phenylethyl)pyridinium iodide, containing both electron-donor and electron-acceptor substituent groups, has a significantly lower E_O than analogs containing a benzyl or benzoyl substituent. This was ascribed to merostabilization of the corresponding radical and it was further supported by theoretical calculations.

To extend these studies beyond pyridinium salts, we chose to look at the properties of sulfonium salts in the gas phase. The available literature on mass spectrometry investigations of sulfonium salts is still very limited since these salts are relatively unstable in the gas phase and can easily fragment to give the corresponding neutral sulfides. Twelve sulfonium salts were studied by ESI FTICR/MS. Collisionally activated dissociation reactions, using neutral argon as the collision gas, were performed to investigate dissociation pathways in the gas phase and to study the stabilizing/destabilizing effect of electron donating/withdrawing substituents on the sulfonium ions. Ion-molecule reactions were performed in order to distinguish between S_N1 and S_N2 reaction mechanisms. Analogous to the pyridinium salts, intermolecular ion-molecule reactions of sulfonium salts were found to be of the S_N1 type.

Only a small fraction of the possible applications of electrospray mass spectrometry has been demonstrated in this thesis. With the constantly improving molecular weight range of detection, electrospray ionization is still developing and achieving better resolution and mass accuracy. New instrumentation, approaches and applications are constantly being reported.

Electrospray ionization, combined with a powerful mass spectrometer such as FTICR, is most commonly used in studying biomolecules, due to its ability to detect and store high-molecular weight species. However, as we have shown, electrospray is also the method of choice for investigation of lower molecular weight species, such as the type of organic salts that we have studied, and in general it can be applied to a variety of organic and inorganic systems.

REFERENCES

The reference citation system employed throughout this dissertation is that from "Comprehensive Heterocyclic Chemistry" (vol. I), Pergamon Press, Oxford, 1984 (editors Alan R. Katritzky and Charles W. Rees).

Each time a reference is cited, a number and letter code appears in brackets, for example [00ABC000]. The first two digits denote the year of the twentieth century, the letter code is an abbreviation for the journal or book cited and the last digits represent the page number.

Additional notes to this reference system are as follows:

(i) References are listed consecutively by year, alphabetically by the journal code and then by page number.

(ii) Each reference code is followed by the conventional literature citation complete with the names of the authors.

(iii) Journals which are published in more than one part, or more than one volume per year, include in the abbreviation cited the appropriate part or volume number.

(iv) Books and journals which are less commonly used are coded "MI" for miscellaneous.

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BIOGRAPHICAL SKETCH

Petia Anastasova Shipkova was born on December 21, 1971, in Sofia, Bulgaria. She completed high school in May, 1989. In the Fall semester of 1989 she was accepted to the Technical University in Sofia, Bulgaria, where she studied chemistry for one year. In the Fall of 1990 she transferred to Park College, Kansas City, Missouri. In 1993 she received her Bachelor of Science degree *summa cum laude* with a double major in chemistry and mathematics.

She started the graduate program in the University of Florida in the Fall of 1993. In January 1994 she joined the research group of Dr. Alan R. Katritzky, and in August 1995 she defended her Master of Science degree and continued her work towards a Ph. D. degree in the same research group. In April 1997 she successfully defended her Ph. D. degree in Analytical Chemistry.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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Kenan Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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May 1997

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